ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 2.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2.5 mg of lenalidomide.

Excipient(s) with known effect:

Each capsule contains 73.5 mg of lactose, anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Blue-green/white capsules marked "REV 2.5 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

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

Myelodysplastic syndromes

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Multiple myeloma

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

- *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.

- *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.

Myelodysplastic syndromes

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

Recommended dose
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment
Dose adjustments, as summarized 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	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days

Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

For patients who experience other toxicities
For other grade 3 or 4 toxicities judged to be related to lenalidomide, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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 and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

The percentage of multiple myeloma 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.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

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.

Patients with renal impairment
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 and multiple myeloma or myelodysplastic syndromes. 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.

- *Multiple myeloma*

Renal Function (CLcr)	**Dose Adjustment** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment ($30 \leq CLcr < 50$ ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

- *Myelodysplastic syndromes*

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment ($30 \leq CLcr < 50$ ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

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

Method of 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.

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, listed in section 6.1.

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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, 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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions
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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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.

In patients with myelodysplatic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – 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 major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. 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. 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. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Multiple myeloma

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).

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).

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

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 SPM 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 SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS
- Karyotype

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest

estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse events tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

The adverse reactions observed in patients treated for multiple myeloma and myelodysplastic syndromes 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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in multiple myeloma and myelodysplastic syndromes and from post-marketing data for multiple myeloma only. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the major clinical trials.

Table 1: ADRs reported in clinical studies and post-marketing data in patients with multiple myeloma and in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections) Common Sepsis, Sinusitis	Common Pneumonia◊+, Bacterial, viral and fungal infections (including opportunistic infections)◊
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome†
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, Iron overload	Common Hypokalaemia, Hypocalcaemia, Hypophosphataemia, Hyperglycaemia◊, Decreased Appetite
Psychiatric Disorder	Uncommon Loss of libido	Common Depression, Altered mood◊~
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, Cardiac failure◊

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Vascular Disorders	Very Common Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ Common Hypotension, Hypertension, Ecchymosis^, Haematoma	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, Bronchitis Not known Interstitial pneumonitis†
Gastrointestinal Disorders	Very Common Constipation, Diarrhoea, Abdominal pain, Nausea, Vomiting Common Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry Mouth, Stomatitis, Dysphagia, Dyspepsia Uncommon Colitis, Caecitis	Common Diarrhoea◊, Constipation, Nausea, Toothache Not known Pancreatitis†
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^, Cytolytic hepatitis^†, Cholestatic hepatitis^†, Mixed cytolytic/ cholestatic hepatitis^†	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^†
Skin and Subcutaneous tissue Disorders	Very Common Rashes, Dry Skin, Pruritus Common Urticaria, Hyperhidrosis, Skin Hyperpigmentation, Eczema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes, Pruritus Uncommon Angioedema† Rare Stevens-Johnson Syndrome^†, Toxic epidermal necrolysis^†
Musculoskeletal and connective tissue disorders	Very Common Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia, Myalgia Common Joint swelling	Common Muscle Weakness, Bone Pain, Back 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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest Pain, Lethargy	Common Fatigue, Pyrexia, Fall
Injury, poisoning and procedural complications	Common Contusion^	

^see section 4.8 description of selected adverse reactions
‡reports from post-marketing data
◊Adverse events reported as serious in myelodysplastic syndromes clinical trials.
+Pneumonia was reported as a very common serious adverse event in the myelodysplastic syndromes Phase II study
~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event
Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

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

- *Multiple myeloma*

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).

- *Myelodysplastic syndromes*

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients with myelodysplastic syndromes treated with lenalidomide monotherapy (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
SJS and 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.

Acute myeloid leukaemia

- *Multiple myeloma*

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

- *Myelodysplastic syndromes*

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.
In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53

negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in 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: L04AX04.

Mechanism of action
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.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Clinical efficacy and safety

Multiple myeloma

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.

Myelodysplastic Syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 2: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

Endpoint	**MDS-004 N = 205**			**MDS-003 N = 148**
	10 mg[†] N = 69	**5 mg[††] N = 69**	**Placebo* N = 67**	**10 mg N = 148**
Transfusion Independence (≥ 182 days)[#]	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)

Transfusion Independence (≥ 56 days) [#]	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to Transfusion Independence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR[∞]	NR	NR	114.4
Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
[#]Associated with an increase in Hgb of ≥ 1g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

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 main multiple myeloma and myelodysplastic syndromes 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 substance (see section 4.4).

Biotransformation and elimination
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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 7 or 21 capsules.

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/1/07/391/005
EU/1/07/391/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of lenalidomide.

Excipient(s) with known effect:

Each capsule contains 147 mg of lactose, anhydrous.

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

Multiple myeloma

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

Myelodysplastic syndromes

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Multiple myeloma

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

- *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.

- *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.

Myelodysplastic syndromes

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

Recommended dose
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment
Dose adjustments, as summarized 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	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days

Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

For patients who experience other toxicities
For other grade 3 or 4 toxicities judged to be related to lenalidomide, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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 and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

The percentage of multiple myeloma 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.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

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.

Patients with renal impairment
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 and multiple myeloma or myelodysplastic syndromes. 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.

- *Multiple myeloma*

Renal Function (CLcr)	**Dose Adjustment** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

- *Myelodysplastic syndromes*

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

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

Method of 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.

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, listed in section 6.1.

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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, 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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions
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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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.

In patients with myelodysplatic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – 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 major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. 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. 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. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Multiple myeloma

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).

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).

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

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 SPM 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 SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

- Karyotype

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest

estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse events tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

The adverse reactions observed in patients treated for multiple myeloma and myelodysplastic syndromes 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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in multiple myeloma and myelodysplastic syndromes and from post-marketing data for multiple myeloma only. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the major clinical trials.

Table 1: ADRs reported in clinical studies and post-marketing data in patients with multiple myeloma and in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections) Common Sepsis, Sinusitis	Common Pneumonia◊+, Bacterial, viral and fungal infections (including opportunistic infections)◊
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome†
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, Iron overload	Common Hypokalaemia, Hypocalcaemia, Hypophosphataemia, Hyperglycaemia◊, Decreased Appetite
Psychiatric Disorder	Uncommon Loss of libido	Common Depression, Altered mood◊~
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, Cardiac failure◊

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Vascular Disorders	Very Common Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ Common Hypotension, Hypertension, Ecchymosis^, Haematoma	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, Bronchitis Not known Interstitial pneumonitis†
Gastrointestinal Disorders	Very Common Constipation, Diarrhoea, Abdominal pain, Nausea, Vomiting Common Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry Mouth, Stomatitis, Dysphagia, Dyspepsia Uncommon Colitis, Caecitis	Common Diarrhoea◊, Constipation, Nausea, Toothache Not known Pancreatitis†
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^, Cytolytic hepatitis^†, Cholestatic hepatitis^†, Mixed cytolytic/ cholestatic hepatitis^†	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^†
Skin and Subcutaneous tissue Disorders	Very Common Rashes, Dry Skin, Pruritus Common Urticaria, Hyperhidrosis, Skin Hyperpigmentation, Eczema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes, Pruritus Uncommon Angioedema† Rare Stevens-Johnson Syndrome^†, Toxic epidermal necrolysis^†
Musculoskeletal and connective tissue disorders	Very Common Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia, Myalgia Common Joint swelling	Common Muscle Weakness, Bone Pain, Back 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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest Pain, Lethargy	Common Fatigue, Pyrexia, Fall
Injury, poisoning and procedural complications	Common Contusion^	

^see section 4.8 description of selected adverse reactions
‡reports from post-marketing data
◊Adverse events reported as serious in myelodysplastic syndromes clinical trials.
+Pneumonia was reported as a very common serious adverse event in the myelodysplastic syndromes Phase II study
~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event
Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

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

- *Multiple myeloma*

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).

- *Myelodysplastic syndromes*

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients with myelodysplastic syndromes treated with lenalidomide monotherapy (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
SJS and 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.

Acute myeloid leukaemia

- *Multiple myeloma*

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

- *Myelodysplastic syndromes*

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.
In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53

negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in 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: L04AX04.

Mechanism of action
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.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Clinical efficacy and safety

Multiple myeloma

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.

Myelodysplastic Syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 2: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

Endpoint	**MDS-004 N = 205**			**MDS-003 N = 148**
	10 mg[†] N = 69	**5 mg[††] N = 69**	**Placebo* N = 67**	**10 mg N = 148**
Transfusion Independence (≥ 182 days)[#]	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)

Transfusion Independence (≥ 56 days) [#]	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to Transfusion Independence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR[∞]	NR	NR	114.4
Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
[#]Associated with an increase in Hgb of ≥ 1g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

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 main multiple myeloma and myelodysplastic syndromes 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 substance (see section 4.4).

Biotransformation and elimination
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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 7 or 21 capsules.

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
EU/1/07/391/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 7.5 mg of lenalidomide.

Excipient(s) with known effect:

Each capsule contains 144.5 mg of lactose, anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pale yellow/white capsules marked "REV 7.5 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

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) $< 1.0 \times 10^9$/l, and/or platelet counts $< 75 \times 10^9$/l or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9$/l.

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

- *Dose reduction steps*

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

- *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.

- *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.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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.

Patients with renal impairment
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** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment ($30 \leq CLcr < 50$ ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

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

Method of 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.

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, listed in section 6.1.

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 $\geq$ 50 years and naturally amenorrhoeic for $\geq$ 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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions

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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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 SPM 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 SPM and institute treatment as indicated.

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.
Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation

(40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Tabulated list of adverse reactions

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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the pivotal studies and from post-marketing data. 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 and post-marketing data 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 (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome‡
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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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 Not known Interstitial pneumonitis‡
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 Not known Pancreatitis‡
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^, Cytolytic hepatitis^‡, Cholestatic hepatitis^‡, Mixed cytolytic/ cholestatic hepatitis^‡	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^‡

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 Uncommon Angioedema‡ Rare Stevens-Johnson Syndrome^‡, Toxic epidermal necrolysis^‡
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 4.8 description of selected adverse reactions
‡reports from post-marketing data

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
SJS and 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.

Acute myeloid leukaemia
Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

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: L04AX04.

Mechanism of action
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 efficacy and safety

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.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 substance (see section 4.4).

Biotransformation and elimination

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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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) 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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 21 capsules.

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/1/07/391/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product 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(s) with known effect:

Each capsule contains 294 mg of lactose, anhydrous.

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

Multiple myeloma

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

Myelodysplastic syndromes

Revlimid is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies (see section 4.4, karyotype).

Posology

Multiple myeloma

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

- *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.

- *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.

Myelodysplastic syndromes

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

Recommended dose
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommended dose adjustments during treatment and restart of treatment
Dose adjustments, as summarized 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	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days

Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

For patients who experience other toxicities
For other grade 3 or 4 toxicities judged to be related to lenalidomide, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.

Discontinuation of lenalidomide

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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 and in myelodysplastic syndromes patients up to 95 years of age (see section 5.1).

The percentage of multiple myeloma 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.

For myelodysplastic syndromes patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

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.

Patients with renal impairment
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 and multiple myeloma or myelodysplastic syndromes. 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.

- *Multiple myeloma*

Renal Function (CLcr)	**Dose Adjustment** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

- *Myelodysplastic syndromes*

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

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

Method of 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.

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, listed in section 6.1.

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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, 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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions
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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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.

In patients with myelodysplatic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma – 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 major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. 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. 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. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

- Multiple myeloma

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).

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).

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

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 SPM 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 SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

- Karyotype

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest

estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes

The overall safety profile of Revlimid in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study (see section 5.1). In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study.

Most adverse events tended to occur during the first 16 weeks of therapy with lenalidomide.

Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Tabulated list of adverse reactions

The adverse reactions observed in patients treated for multiple myeloma and myelodysplastic syndromes 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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the main studies in multiple myeloma and myelodysplastic syndromes and from post-marketing data for multiple myeloma only. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies (see section 5.1).

Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the major clinical trials.

Table 1: ADRs reported in clinical studies and post-marketing data in patients with multiple myeloma and in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections) Common Sepsis, Sinusitis	Common Pneumonia◊+, Bacterial, viral and fungal infections (including opportunistic infections)◊
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome†
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, Iron overload	Common Hypokalaemia, Hypocalcaemia, Hypophosphataemia, Hyperglycaemia◊, Decreased Appetite
Psychiatric Disorder	Uncommon Loss of libido	Common Depression, Altered mood◊~
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, Cardiac failure◊

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Vascular Disorders	Very Common Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ Common Hypotension, Hypertension, Ecchymosis^, Haematoma	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, Bronchitis Not known Interstitial pneumonitis†
Gastrointestinal Disorders	Very Common Constipation, Diarrhoea, Abdominal pain, Nausea, Vomiting Common Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry Mouth, Stomatitis, Dysphagia, Dyspepsia Uncommon Colitis, Caecitis	Common Diarrhoea◊, Constipation, Nausea, Toothache Not known Pancreatitis†
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^, Cytolytic hepatitis^†, Cholestatic hepatitis^†, Mixed cytolytic/ cholestatic hepatitis^†	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^†, Hepatitis toxic^†
Skin and Subcutaneous tissue Disorders	Very Common Rashes, Dry Skin, Pruritus Common Urticaria, Hyperhidrosis, Skin Hyperpigmentation, Eczema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes, Pruritus Uncommon Angioedema† Rare Stevens-Johnson Syndrome^†, Toxic epidermal necrolysis^†
Musculoskeletal and connective tissue disorders	Very Common Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia, Myalgia Common Joint swelling	Common Muscle Weakness, Bone Pain, Back 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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest Pain, Lethargy	Common Fatigue, Pyrexia, Fall
Injury, poisoning and procedural complications	Common Contusion^	

^see section 4.8 description of selected adverse reactions
‡reports from post-marketing data
◊Adverse events reported as serious in myelodysplastic syndromes clinical trials.
+Pneumonia was reported as a very common serious adverse event in the myelodysplastic syndromes Phase II study
~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes Phase III study; it was not reported as a grade 3 or 4 adverse event
Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase III study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo
- Myelodysplastic syndromes Phase II study
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse\events in 1% of lenalidomide treated subjects
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects
- Algorithm applied for inclusion in the SmPC: All ADRs captured by the Phase III study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the Phase II study algorithm was undertaken and, if the frequency of the ADRs in the Phase II study was higher than in the Phase III study, the event was included in the EU SmPC at the frequency it occurred in the Phase II study.

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

- *Multiple myeloma*

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).

- *Myelodysplastic syndromes*

In myelodysplastic syndromes patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (74.6% in lenalidomide-treated patients compared with 14.9% in patients on placebo in the Phase III study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in patients on placebo). Lenalidomide is associated with a higher incidence of grade 3 or 4 thrombocytopenia (37% in lenalidomide-treated patients compared with 1.5% in patients on placebo in the Phase III study).

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients with myelodysplastic syndromes treated with lenalidomide monotherapy (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
SJS and 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.

Acute myeloid leukaemia

- *Multiple myeloma*

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

- *Myelodysplastic syndromes*

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.
In a post-hoc analysis of a clinical trial of Revlimid in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53

negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in 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: L04AX04.

Mechanism of action
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.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

Clinical efficacy and safety

Multiple myeloma

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.

Myelodysplastic Syndromes

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a Phase III, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a Phase II, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately (see section 4.1 for the approved indication).

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

Table 2: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population

Endpoint	**MDS-004 N = 205**			**MDS-003 N = 148**
	10 mg[†] N = 69	**5 mg[††] N = 69**	**Placebo* N = 67**	**10 mg N = 148**
Transfusion Independence (≥ 182 days)[#]	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)

Transfusion Independence (≥ 56 days) [#]	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median Time to Transfusion Independence (weeks)	4.6	4.1	0.3	4.1
Median Duration of Transfusion Independence (weeks)	NR[∞]	NR	NR	114.4
Median Increase in Hgb, g/dL	6.4	5.3	2.6	5.6

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles
†† Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles
* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase
[#]Associated with an increase in Hgb of ≥ 1g/dL
∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma and myelodysplastic syndromes (see section 4.2 for information on paediatric use).

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 main multiple myeloma and myelodysplastic syndromes 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 substance (see section 4.4).

Biotransformation and elimination
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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndromes.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 21 capsules.

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

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product 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(s) with known effect:

Each capsule contains 289 mg of lactose, anhydrous.

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 in adult patients who have received at least one prior therapy.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

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) $< 1.0 \times 10^9$/l, and/or platelet counts $< 75 \times 10^9$/l or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9$/l.

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

- *Dose reduction steps*

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

- *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.

- *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.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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.

Patients with renal impairment
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** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment ($30 \leq CLcr < 50$ ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

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

Method of 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.

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, listed in section 6.1.

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 $\geq$ 50 years and naturally amenorrhoeic for $\geq$ 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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions

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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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 SPM 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 SPM and institute treatment as indicated.

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.
Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation

(40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Tabulated list of adverse reactions

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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the pivotal studies and from post-marketing data. 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 and post-marketing data 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 (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome‡
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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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 Not known Interstitial pneumonitis‡
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 Not known Pancreatitis‡
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^, Cytolytic hepatitis^‡, Cholestatic hepatitis^‡, Mixed cytolytic/ cholestatic hepatitis^‡	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^‡

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 Uncommon Angioedema‡ Rare Stevens-Johnson Syndrome^‡, Toxic epidermal necrolysis^‡
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 4.8 description of selected adverse reactions
‡reports from post-marketing data

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
SJS and 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.

Acute myeloid leukaemia
Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

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: L04AX04.

Mechanism of action
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 efficacy and safety

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.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 substance (see section 4.4).

Biotransformation and elimination

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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 21 capsules.

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

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product 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(s) with known effect:

Each capsule contains 200 mg of lactose, anhydrous.

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 in adult patients who have received at least one prior therapy.

4.2 Posology and method of administration

Revlimid treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Posology

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) $< 1.0 \times 10^9$/l, and/or platelet counts $< 75 \times 10^9$/l or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9$/l.

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

- *Dose reduction steps*

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

- *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.

- *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.

Special populations

Paediatric population
The safety and efficacy of Revlimid in children aged 0-17 years have not yet been established. No data are available.

Elderly population
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.

Patients with renal impairment
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** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment ($30 \leq CLcr < 50$ ml/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	7.5 mg once daily[2,3] 15 mg every other day[3]
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.

[1] 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.
[2] In countries where the 7.5 mg capsule is available.
[3] 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.

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

Method of 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.

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, listed in section 6.1.

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 $\geq$ 50 years and naturally amenorrhoeic for $\geq$ 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 or during lactation 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 contraceptive measures 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 substance 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 not using effective contraception (even if the man has had a vasectomy), during treatment and for 1 week after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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 substance 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 not using effective contraception (even if the man has had a vasectomy).

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, prescribing and dispensing restrictions

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. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. 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 and following a medically supervised negative pregnancy test result.

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 SPM 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 SPM and institute treatment as indicated.

Hepatic Disorders
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.
Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction.

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).

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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side- effects.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 substance 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.

Pregnancy
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).

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

Fertility
A fertility study in rats with lenalidomide doses up to 5000 mg/kg (600 times human dose of 10 mg on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

Lenalidomide has 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

Summary of the safety profile

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 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 with lenalidomide in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation

(40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Tabulated list of adverse reactions

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), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the pivotal studies and from post-marketing data. 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 and post-marketing data 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 (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Rare Tumour lysis syndrome‡
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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
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 Not known Interstitial pneumonitis‡
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 Not known Pancreatitis‡
Hepatobiliary Disorders	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^, Cytolytic hepatitis^‡, Cholestatic hepatitis^‡, Mixed cytolytic/ cholestatic hepatitis^‡	Common Abnormal Liver Function Tests Uncommon Hepatic failure^ Not known Acute hepatic failure^‡, Hepatitis toxic^‡

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 Uncommon Angioedema‡ Rare Stevens-Johnson Syndrome^‡, Toxic epidermal necrolysis^‡
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 4.8 description of selected adverse reactions
‡reports from post-marketing data

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
SJS and 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.

Acute myeloid leukaemia
Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following high dose melphalan and ASCT (see section 4.4).

Hepatic disorders
The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

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: L04AX04.

Mechanism of action
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 efficacy and safety

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.

The European Medicines Agency has waived the obligation to submit the results of studies with Revlimid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 substance (see section 4.4).

Biotransformation and elimination

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 doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma.

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. 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. Approximately 30% of the drug in the body was removed during a single 4-hour dialysis session. 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 colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

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

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

Pack size of 21 capsules.

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

Date of first authorisation: 14 June 2007
Date of first renewal: 14 June 2012

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) 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 OR RESTRICTIONS REGARDING THE SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

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 (and where appropriate, and in agreement with the National Competent Authority, prior to 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:
    - The details of the implementation of the MDS Post-Authorisation Safety Study (MDS PASS)
    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communications

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 risk of progression to AML in MDS patients including incidence rates from clinical trials
- 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 not using effective contraceptions (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
- Details on the MDS PASS emphasizing that prior to prescribing Revlimid, the healthcare professionals should enroll MDS patients into the PASS.
- 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
- That Revlimid may cause venous and arterial thromboembolism
- 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
- That a study is being conducted to collect information regarding the safety of the drug and to monitor its appropriate use; and that MDS patients should be included in the study prior to the start of the treatment with Revlimid

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 not using effective contraceptions (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

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

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
A post-authorisation non-interventional, safety study of patients with myelodysplastic syndromes (MDS) treated with lenalidomide to gather safety data on the use of lenalidomide in MDS patients and monitor off-label use.	Annual safety updates with PSURs

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 2.5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2.5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 or 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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/1/07/391/005
EU/1/07/391/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 2.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 2.5 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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.

4. PHARMACEUTICAL FORM AND CONTENTS

7 or 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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
EU/1/07/391/008

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

BLISTERS

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

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 7.5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose.

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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/1/07/391/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 7.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 7.5 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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.

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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

BLISTERS

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

5. OTHER

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.

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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

BLISTERS

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

5. OTHER

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.

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

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

BLISTERS

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

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Revlimid 2.5 mg hard capsules
Revlimid 5 mg hard capsules
Revlimid 10 mg hard capsules
lenalidomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours**.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Revlimid is and what it is used for

What Revlimid is
Revlimid contains the active substance 'lenalidomide'. This medicine belongs to a group of medicines which affect how your immune system works.

What Revlimid is used for

Multiple myeloma
- Revlimid is used with another medicine called 'dexamethasone' (an anti-inflammatory medicine) to treat adults with a type of cancer called multiple myeloma. It is used when you have already had one or more other types of treatment before.

Myelodysplastic syndromes
Revlimid is also used alone to treat adult patients who have been diagnosed with myelodysplastic syndromes, when all of the following apply:
- you need regular blood transfusions to treat low levels of red blood cells ('transfusion-dependent anaemia')
- you have an abnormality of cells in the bone marrow called an 'isolated deletion 5q cytogenic abnormality' . This means you do not make enough healthy blood cells
- other treatments have been used before, are not suitable or do not work well enough.

What is multiple myeloma
Multiple myeloma is a type of cancer which affects a certain type of white blood cell, called the plasma cell. These cells collect in the bone marrow and divide out of control. This can damage the bone and kidneys.

Multiple myeloma generally cannot be cured. However, the signs and symptoms can be greatly reduced or disappear for a period of time. This is called a 'remission'.

What are myelodysplastic syndromes
Myelodysplastic syndromes (MDS) are a collection of many different blood and bone marrow diseases. The blood cells become abnormal and do not function properly. Patients can experience a variety of signs and

symptoms including a low red blood cell count (anaemia), the need for a blood transfusion, and a risk of infection.

How Revlimid works
Revlimid works by affecting the body's immune system and directly attacking the cancer. It works in a number of different ways:

- by stopping the cancer cells developing
- by stopping blood vessels growing in the cancer
- by stimulating part of the immune system to attack the cancer cells.

Multiple Myeloma
Revlimid can stop the signs and symptoms of multiple myeloma getting worse:

- Revlimid delayed the recurrence of multiple myeloma for up to 48 weeks compared to 20 weeks for those who were not taking Revlimid.

Myelodysplastic syndromes
Revlimid can increase the number of healthy red blood cells that the body produces by reducing the number of abnormal cells:

- This can reduce the number of blood transfusions needed. It is possible that no transfusions will be needed.

2. What you need to know before you take Revlimid

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, "Warnings and precautions" and "Pregnancy and breast-feeding").
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2, "Warnings and precautions" and "Pregnancy and breast-feeding"). 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 to lenalidomide or any of the other ingredients of this medicine listed in section 6. 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.

Warnings and precautions
Talk to your doctor or pharmacist before taking Revlimid.

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 every treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except where it has been confirmed that the fallopian tubes have been severed and sealed, to stop eggs from reaching the uterus (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 does not use effective methods of contraception, you must use condoms during treatment and 1 week after the end of treatment, even if you have had a vasectomy.

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 (white blood cells) and help the blood to clot (platelets). 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.

Please tell your doctor if you have:
- had a heart attack, have ever had a blood clot, or if you smoke, have high blood pressure or high cholesterol levels.
- a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure (this condition is called Tumour Lysis Syndrome).
- had an allergic reaction whilst taking thalidomide such as rash, itching, swelling, dizziness or trouble breathing.

If you have myelodysplastic syndromes, you may be more likely to get a more advanced condition called acute myeloid leukaemia (AML). In addition, we do not know how Revlimid affects the chances of you getting AML. Your doctor may therefore do tests to check for signs which may better predict the likelihood of getting AML during your treatment with Revlimid.

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

Children and adolescents
Revlimid is not recommended for use in children and young people under 18 years.

Other medicines and Revlimid
Tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription including herbal medicines. This is because Revlimid can affect the way some other medicines work. Also, some other medicines can affect the way Revlimid works.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- some medicines used to prevent pregnancy such as oral contraceptives, as they may stop working
- some medicines used for heart problems – such as digoxin
- some medicines used to thin the blood – such as warfarin

Pregnancy and breast-feeding

Pregnancy

For women taking Revlimid
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, "What you need to know before you take 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
For men taking Revlimid, please see section 2, "What you need to know before you take 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 breast-feed 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.

Revlimid contains lactose
Revlimid contains lactose. 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 must be given to you by healthcare professionals with experience in treating multiple myeloma or myelodysplastic syndromes.

When used to treat multiple myeloma, Revlimid is taken in combination with dexamethasone. When used to treat myelodysplastic syndromes, it is taken alone. Always take Revlimid alone or Revlimid and dexamethasone in combination exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. You should refer to the package leaflet of dexamethasone for further information on its use and effects.

Multiple myeloma

Revlimid dose

The recommended 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, "What you need to know before you take Revlimid").

Dexamethasone dose
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.

Myelodysplastic syndromes

Revlimid dose
The usual starting dose is 10 mg once per day. Revlimid is taken in treatment cycles, each cycle lasting 28 days.

Treatment cycle:
- On days 1-21: take 10 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, "What you need to know before you take Revlimid").

All patients

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 "Treatment cycle"). 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 this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Revlimid can cause side effects, although not everybody gets them.

Serious side effects which may affect more than 1 in 10 people
Revlimid may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders e.g. nosebleeds and bruising. Revlimid may also cause blood clots in the veins (thrombosis).

Therefore **you must tell your doctor immediately** if you experience:
- fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection
- bleeding or bruising in the absence of injury
- chest pain or leg pain
- shortness of breath

Other side effects are given below
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 may affect more than 1 in 10 people:
- A fall in the number of red blood cells which may cause anaemia leading to tiredness and weakness
- Constipation, diarrhoea, nausea, redness of skin, rashes, vomiting, muscle cramps, muscle aches, bone pain, joint pain, tiredness, generalised swelling including swelling of the limbs
- Fever and flu like symptoms including fever, muscle ache, headache, earache 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, called pulmonary embolism)
- Infections of all types
- Infection of the lung and the upper respiratory tract, shortness of breath
- Blurred vision
- Headache
- Dry skin
- Abdominal pain

Common side effects may affect up to 1 in 10 people:
- Infection of the sinuses that surround the nose
- Bleeding from the gums, stomach, or bowels
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Increased pigmentation of skin
- Skin eruptions, skin cracking, flaking or peeling skin
- Hives, itching, increased sweating, dehydration
- Sore inflamed mouth, dry mouth, difficulty swallowing
- Heartburn
- 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)
- Iron overload
- Thirst
- Mood change
- Confusion
- Toothache

Uncommon side effects may affect up to 1 in 100 people:
- Bleeding within the skull
- Circulatory problems
- Loss of vision
- Loss of sex drive (libido)
- Passing large amount of urine with bone pain and weakness, which may be symptoms of a kidney disorder (Fanconi syndrome)
- Inflammation of the large intestine (colitis and caecitis), 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 discolouration, sensitivity to sunlight
- Certain types of skin tumour
- Types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty breathing, or itching (hypersensitivity/angioedema)

Rare side effects may affect up to 1 in 1,000 people:
- Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).
- 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.

Not known: frequency cannot be estimated from the available data:
- 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.
- Yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale coloured stools, dark coloured urine, skin itch, rash, pain or swelling of the abdomen –these may be symptoms of injury to the liver (hepatic disorder).

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Revlimid

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the blister after "EXP". The expiry date refers to the last day of that month.
- Do not use this medicine if you notice any damage or signs of tampering to the pack.
- Do not throw away any medicines via wastewater or household waste. All unused Revlimid capsules should be returned to the pharmacist. These measures will help protect the environment.

6. Content of the pack and other information

What Revlimid contains

Revlimid 2.5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 2.5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; 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 5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; 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: lactose, anhydrous; cellulose, microcrystalline; 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).

What Revlimid looks like and contents of the pack

Revlimid 2.5 mg hard capsules are blue-green/white, with "REV 2.5 mg" written on them.
The capsules are provided in packs. Each pack contains one or three blisters, each blister with seven capsules. This gives a total of 7 or 21 capsules per pack.

Revlimid 5 mg hard capsules are white, with "REV 5 mg" written on them.
The capsules are provided in packs. Each pack contains one or three blisters, each blister with seven capsules. This gives a total of 7 or 21 capsules per pack.

Revlimid 10 mg hard capsules are blue-green/pale yellow, with "REV 10 mg" written on them.
The capsules are provided in packs. Each pack contains three blisters, each blister with seven capsules. This gives a total of 21 capsules per pack.

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Celgene Europe Limited
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Uxbridge
UB11 1DB
United Kingdom

Marketing Authorisation Holder
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United Kingdom

Manufacturer
Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
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Gwent
NP22 3AA
United Kingdom

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United Kingdom

This leaflet was last revised in

Other sources of information:

Please contact the Marketing Authorisation Holder if you require this information in another format.

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

There are also links to other websites about rare diseases and treatments.

Package leaflet: Information for the patient

Revlimid 7.5 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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours**.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Revlimid is and what it is used for

What Revlimid is
Revlimid contains the active substance 'lenalidomide'. This medicine belongs to a group of medicines which affect how your immune system works.

What Revlimid is used for
Revlimid is used with another medicine called 'dexamethasone' (an anti-inflammatory medicine) to treat adults with a type of cancer called multiple myeloma. It is used when you have already had one or more other types of treatment before.

What is multiple myeloma
Multiple myeloma is a type of cancer which affects a certain type of white blood cell, called the plasma cell. These cells collect in the bone marrow and divide out of control. This can damage the bone and kidneys.

Multiple myeloma generally cannot be cured. However, the signs and symptoms can be greatly reduced or disappear for a period of time. This is called a 'remission'.

How Revlimid works
Revlimid works by affecting the body's immune system and directly attacking the cancer. It works in a number of different ways:
- by stopping the cancer cells developing
- by stopping blood vessels growing in the cancer
- by stimulating part of the immune system to attack the cancer cells.

Revlimid can stop the signs and symptoms of multiple myeloma getting worse:
- Revlimid delayed the recurrence of multiple myeloma for up to 48 weeks compared to 20 weeks for those who were not taking Revlimid.

2. What you need to know before you take Revlimid

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, "Warnings and precautions" and "Pregnancy and breast-feeding").
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2, "Warnings and precautions" and "Pregnancy and breast-feeding"). 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 to lenalidomide or any of the other ingredients of this medicine listed in section 6. 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.

Warnings and precautions
Talk to your doctor or pharmacist before taking Revlimid.

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 every treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except where it has been confirmed that the fallopian tubes have been severed and sealed, to stop eggs from reaching the uterus (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 does not use effective methods of contraception, you must use condoms during treatment and 1 week after the end of treatment, even if you have had a vasectomy.

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 (white blood cells) and help the blood to clot (platelets). 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.

Please tell your doctor if you have:
- had a heart attack, have ever had a blood clot, or if you smoke, have high blood pressure or high cholesterol levels.
- a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure (this condition is called Tumour Lysis Syndrome).
- had an allergic reaction whilst taking thalidomide such as rash, itching, swelling, dizziness or trouble breathing.

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

Children and adolescents
Revlimid is not recommended for use in children and young people under 18 years.

Other medicines and Revlimid
Tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription including herbal medicines. This is because Revlimid can affect the way some other medicines work. Also, some other medicines can affect the way Revlimid works.

In particular, tell your doctor or nurse if you are taking any of the following medicines:
- some medicines used to prevent pregnancy such as oral contraceptives, as they may stop working
- some medicines used for heart problems – such as digoxin
- some medicines used to thin the blood – such as warfarin

Pregnancy and breast-feeding

Pregnancy

For women taking Revlimid
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, "What you need to know before you take 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
For men taking Revlimid, please see section 2, "What you need to know before you take 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 breast-feed 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.

Revlimid contains lactose
Revlimid contains lactose. 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 must be given to you by healthcare professionals with experience in treating multiple myeloma.

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

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

Revlimid dose

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, "What you need to know before you take Revlimid").

Dexamethasone dose
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.

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 "Treatment cycle"). 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 this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Revlimid can cause side effects, although not everybody gets them.

Serious side effects which may affect more than 1 in 10 people
Revlimid may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets) which may lead to bleeding disorders e.g. nosebleeds and bruising. Revlimid may also cause blood clots in the veins (thrombosis).

Therefore **you must tell your doctor immediately** if you experience:
- fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection
- bleeding or bruising in the absence of injury
- chest pain or leg pain
- shortness of breath

Other side effects are given below
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 may affect more than 1 in 10 people:
- A fall in the number of red blood cells which may cause 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, called pulmonary embolism)
- Infection of the lung and the upper respiratory tract, shortness of breath
- Blurred vision
- Headache

Common side effects may affect up to 1 in 10 people:
- Infections of all types
- Infection of the sinuses that surround the nose
- Bleeding from the gums, stomach, or bowels
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Increased pigmentation of skin
- Skin eruptions, skin cracking, flaking or peeling skin
- 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 may affect up to 1 in 100 people:
- Bleeding within the skull
- Circulatory problems
- Loss of vision
- Loss of sex drive (libido)
- Passing large amount of urine with bone pain and weakness, which may be symptoms of a kidney disorder (Fanconi syndrome)
- Inflammation of the large intestine (colitis and caecitis), 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 discolouration, sensitivity to sunlight
- Certain types of skin tumour
- Types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty breathing, or itching (hypersensitivity/angioedema)

Rare side effects may affect up to 1 in 1,000 people:
- Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body (Stevens-Johnson syndrome and/or toxic epidermal necrolysis).
- 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.

Not known: frequency cannot be estimated from the available data:
- 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.
- Yellow pigmentation to the skin, mucus membrane or eyes (jaundice), pale coloured stools, dark coloured urine, skin itch, rash, pain or swelling of the abdomen –these may be symptoms of injury to the liver (hepatic disorder).

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Revlimid

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the blister after “EXP”. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice any damage or signs of tampering to the pack.

- Do not throw away any medicines via wastewater or household waste. All unused Revlimid capsules should be returned to the pharmacist. These measures will help protect the environment.

6. Content of the pack and other information

What Revlimid contains

Revlimid 7.5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 7.5 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: lactose, anhydrous; cellulose, microcrystalline; croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171) 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: lactose, anhydrous; cellulose, microcrystalline; 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: lactose, anhydrous; cellulose, microcrystalline; 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 7.5 mg hard capsules are pale yellow/white, with “REV 7.5 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 blister with seven capsules. This gives a total of 21 capsules per pack.

Marketing Authorisation Holder and Manufacturer
Celgene Europe Limited
1 Longwalk Road
Stockley Park
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UB11 1DB
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Marketing Authorisation Holder
Celgene Europe Limited
1 Longwalk Road
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Manufacturer
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Celgene Europe Limited
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This leaflet was last revised in

Other sources of information:

Please contact the Marketing Authorisation Holder if you require this information in another format.

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

There are also links to other websites about rare diseases and treatments.

Annex IV

Conclusions on the request for one-year marketing protection presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the Marketing Authorisation Holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing as further explained in the European Public Assessment Report.