

Revlimid[®]▼ (lenalidomide)

SUMMARY OF PRODUCT CHARACTERISTICS

Date of approval of this version (14.0) by European Commission:
April 2010

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules

Revlimid 10 mg hard capsules

Revlimid 15 mg hard capsules

Revlimid 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Revlimid 5 mg hard capsule contains 5 mg of lenalidomide.

Excipient: Each capsule contains 147 mg of anhydrous lactose.

Each Revlimid 10 mg hard capsule contains 10 mg of lenalidomide.

Excipient: Each capsule contains 294 mg of anhydrous lactose.

Each Revlimid 15 mg hard capsule contains 15 mg of lenalidomide.

Excipient: Each capsule contains 289 mg of anhydrous lactose.

Each Revlimid 25 mg hard capsule contains 25 mg of lenalidomide.

Excipient: Each capsule contains 200 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Revlimid 5 mg hard capsules: White capsules marked "REV 5 mg".

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

Revlimid 15 mg hard capsules: Pale blue/white capsules marked "REV 15 mg".

Revlimid 25 mg hard capsules: White capsules marked "REV 25 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Administration

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

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28 day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28 day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

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

Recommended dose adjustments during treatment and restart of treatment

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

• *Dose reduction steps*

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

• *Platelet counts*

Thrombocytopenia

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

- *Absolute Neutrophil counts (ANC)*

Neutropenia

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

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

Paediatric patients

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

Elderly patients

The effects of age on the pharmacokinetics of lenalidomide have not been studied. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 86 years of age (see section 5.1). The percentage of patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Use in patients with impaired renal function

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

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

Renal Function (CLcr)	Dose Adjustment
Moderate renal impairment ($30 \leq \text{CLcr} < 50$ ml/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day**
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis

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

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

Use in patients with impaired hepatic function

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy warning

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

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

Criteria for women of non-childbearing potential

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

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

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

Counselling

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

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

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:

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

The prescriber must ensure that for women of childbearing potential:

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

Contraception

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

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

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

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception

the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

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

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

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment

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

Follow-up and end of treatment

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

Men

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Additional precautions

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

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

Educational materials

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

Other special warnings and precautions for use

Cardiovascular disorders

Venous thromboembolism

The combination of lenalidomide with dexamethasone is associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma (see sections 4.5 and 4.8). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 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, such as low molecular weight heparins or warfarin, should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

Myocardial Infarction

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Oral contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of drugs, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

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

Warfarin

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

Digoxin

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

4.6 Pregnancy and lactation

Pregnancy (see also sections 4.3 and 4.4)

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

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

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination. The median duration of exposure to study treatment was significantly longer (44.0 weeks) in the lenalidomide/dexamethasone group as compared to placebo/dexamethasone (23.1 weeks). The difference was accounted for by a lower rate of discontinuation from study treatment due to lower progression of disease in patients exposed to lenalidomide/dexamethasone (39.7%) than in placebo/dexamethasone patients (70.4%).

325 (92%) of the patients in the lenalidomide/dexamethasone group experienced at least one adverse reaction compared to 288 (82%) in the placebo/dexamethasone group.

The most serious adverse reactions were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

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

The adverse reactions observed in patients treated with lenalidomide/dexamethasone are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$ including isolated reports), unknown (cannot be estimated from the available data). In the majority of cases, there was no significant difference in the incidence of specific adverse events between the two treatment arms. Only those adverse reactions marked with * occurred significantly more frequently in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm.

The following adverse reactions have been observed in clinical trials and postmarketing experience:

Reports from post-marketing experience are marked with †

Infections and infestations

Common: Pneumonia*, lower respiratory tract infection, Herpes Zoster, *Herpes Simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, oral candidiasis, oral fungal infection

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

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Basal cell carcinoma, glioblastoma multiforme

Rare: Tumour lysis syndrome

Blood and lymphatic system disorders

Very Common: Anaemia*, neutropenia*, thrombocytopenia*, haemorrhagic disorder

Common: Febrile neutropenia, pancytopenia, leucopenia*, lymphopenia*

Uncommon: Granulocytopenia, haemolytic anaemia, autoimmune haemolytic anaemia, haemolysis, hypercoagulation, coagulopathy, monocytopenia, leucocytosis, lymphadenopathy

Immune system disorders

Uncommon: Acquired hypogammaglobulinaemia

Rare: Hypersensitivity reaction

Endocrine disorders

Common: Cushingoid-like symptoms

Uncommon: Adrenal suppression, adrenal insufficiency, acquired hypothyroidism, increased and decreased thyroid stimulating hormone, hirsutism

Metabolism and nutrition disorders

Common: Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention

Uncommon: Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, failure to thrive, gout, hypophosphataemia, hyperphosphataemia, increased appetite

Psychiatric disorders

Very Common: Insomnia

Common: Confusional state, hallucinations, depression, aggression, agitation, mood alteration, anxiety, nervousness, irritability, mood swings

Uncommon: Psychotic disorder, hypomania, delusion, mental status changes, sleep disorder, abnormal dreams, depressed mood, affect lability, listless, loss of libido, nightmare, personality change, panic attack, restlessness.

Nervous system disorders

Common: Cerebrovascular accident, syncope, peripheral neuropathy, neuropathy, peripheral sensory neuropathy, dizziness, ageusia, dysgeusia, paraesthesia, headache, tremor*, hypoaesthesia*, somnolence, memory impairment

Uncommon: Intracranial haemorrhage, intracranial venous sinus thrombosis, thrombotic stroke, cerebral ischaemia, transient ischaemic attack, leukoencephalopathy, neurotoxicity, polyneuropathy, peripheral motor neuropathy, dysaesthesia, aphonia, dysphonia, disturbance in attention, ataxia, balance impaired, postural dizziness, burning sensation, cervical root pain, dyskinesia, hyperaesthesia, motor dysfunction, myasthenic syndrome, oral paraesthesia, psychomotor hyperactivity, anosmia

Eye disorders

Common: Blurred vision, cataract, reduced visual acuity, lacrimation increased

Uncommon: Blindness, retinal arteriosclerosis, retinal vein thrombosis, keratitis, visual disturbance, eyelid oedema, conjunctivitis, eye pruritus, eye redness, eye irritation, dry eye

Ear and labyrinth disorders

Common: Vertigo

Uncommon: Deafness, hypoacusia, tinnitus, ear pain, ear pruritus

Cardiac disorders

- Common: Atrial fibrillation, palpitations, myocardial infarction[†]
Uncommon: Congestive cardiac failure, pulmonary oedema, heart valve insufficiency, atrial flutter, arrhythmia, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, sinus tachycardia

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

- Common: Pulmonary embolism, dyspnoea*, exertional dyspnoea, bronchitis, cough, pharyngitis, nasopharyngitis, hoarseness, hiccups, epistaxis
Uncommon: Bronchopneumopathy, asthma, respiratory distress, pulmonary congestion, pleuritic pain, nasal congestion, throat secretion increased, laryngitis, sinus congestion, sinus pain, rhinorrhoea, dry throat
Unknown: Interstitial pneumonitis[†]

Gastrointestinal disorders

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

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

- Very common: Rash*
Common: Face oedema, dry skin, pruritus*, erythema, folliculitis, skin hyperpigmentation, exanthema, increased sweating, night sweats, alopecia
Uncommon: Erythema nodosum, urticaria, angioedema[†], eczema, erythroderma, erythematous rash, pruritic rash, papular rash, hyperkeratosis, skin fissures, acne, dermatitis acneiforme, lichen sclerosus, decubitus ulcer, pigmentation lip, prurigo, rosacea, photosensitivity reaction, seborrheic dermatitis, skin burning sensation, skin desquamation, skin discolouration
Rare: Stevens-Johnson syndrome[†], toxic epidermal necrolysis[†]

Musculoskeletal and connective tissue disorders

- Very Common: Muscle cramp*, muscle weakness
Common: Steroid myopathy, myopathy, myalgia, arthralgia, back pain, bone pain, pain in limb, chest wall pain, peripheral swelling

Uncommon: Osteonecrosis, muscle atrophy, amyotrophy, pain in foot, muscle spasms, musculoskeletal pain, night cramps, groin pain, pain in jaw, neck pain, spondylitis, joint stiffness, joint swelling, musculoskeletal stiffness, limb discomfort, toe deformities, local swelling

Renal and urinary disorders

Common: Renal failure, haematuria

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

Reproductive system and breast disorders

Common: Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain

Congenital, familial and genetic disorders

Uncommon: Chromosome abnormality

General disorders and administration site conditions

Very Common: Fatigue*, asthenia*, peripheral oedema

Common: Pyrexia, rigors, mucosal inflammation, oedema, lethargy, malaise

Uncommon: Hyperpyrexia, chest pain, chest tightness, pain, difficulty in walking, abnormal gait, thirst, chest pressure sensation, feeling cold, feeling jittery, influenza-like illness, submandibular mass, fall, impaired healing

Investigations

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

Injury, poisoning and procedural complications

Common: Contusion

Uncommon: Wound complication

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).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Clinical trials

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

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

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

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

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior ($p < 0.00001$) to dexamethasone alone for the primary efficacy endpoint, TTP (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.

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

In vitro (¹⁴C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively. Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug (see section 4.4).

Metabolism and excretion

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

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

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

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

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy. Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral

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

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

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Revlimid 5 mg hard capsules:

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

Revlimid 10 mg hard capsules:

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

Revlimid 15 mg hard capsules:

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

Revlimid 25 mg hard capsules:

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

Capsule shell: Gelatin
Titanium dioxide (E171)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

Unused medicinal product should be returned to the pharmacist.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Riverside House
Riverside Walk
Windsor
Berkshire
SL4 1NA
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Revlimid 5 mg hard capsules EU/1/07/391/001
Revlimid 10 mg hard capsules EU/1/07/391/002
Revlimid 15 mg hard capsules EU/1/07/391/003
Revlimid 25 mg hard capsules EU/1/07/391/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2007

10. DATE OF REVISION OF THE TEXT

23/03/2010

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