AUSTRALIAN PRODUCT INFORMATION
REVLIMID® (lenalidomide) capsules

Teratogenic Effects:
Revlimid (lenalidomide) is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Women should be advised to avoid pregnancy whilst taking Revlimid (lenalidomide), during dose interruptions, and for 4 weeks after stopping the medication.

1. NAME OF THE MEDICINE

Australian approved name: lenalidomide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5 mg capsule contains 2.5 mg lenalidomide and 73.5 mg of lactose (as anhydrous lactose).
Each 5 mg capsule contains 5 mg lenalidomide and 147 mg of lactose (as anhydrous lactose).
Each 7.5 mg capsule contains 7.5 mg lenalidomide and 144.5 mg of lactose (as anhydrous lactose).
Each 10 mg capsule contains 10 mg lenalidomide and 294 mg of lactose (as anhydrous lactose).
Each 15 mg capsule contains 15 mg lenalidomide and 289 mg of lactose (as anhydrous lactose).
Each 20 mg capsule contains 20 mg lenalidomide and 244.5 mg of lactose (as anhydrous lactose).
Each 25 mg capsule contains 25 mg lenalidomide and 200 mg of lactose (as anhydrous lactose).

For the full list of excipients, see section 6.1 (List of excipients).

Description

Lenalidomide is an off-white to pale-yellow solid, with a melting point between 265ºC and 270ºC. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer. The solubility of lenalidomide in water and at pH 1.21 is < 1.5 mg/mL and 18 mg/mL, respectively.

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 with a net optical rotation of zero.

3. PHARMACEUTICAL FORM

Revlimid (lenalidomide) 2.5 mg capsules: white/blue-green size 4 capsules marked “2.5 mg REV”.
Revlimid (lenalidomide) 5 mg capsules: white size 2 capsules marked “5 mg REV”.
Revlimid (lenalidomide) 7.5 mg capsules: white/pale-yellow size 2 capsules marked “7.5 mg REV”.
Revlimid (lenalidomide) 10 mg capsules: yellow/blue-green size 0 capsules marked “10 mg REV”.
Revlimid (lenalidomide) 15 mg capsules: white/blue size 0 capsules marked “15 mg REV”.
Revlimid (lenalidomide) 20 mg capsules: powder-blue/blue-green size 0 capsules marked “20 mg REV”.
Revlimid (lenalidomide) 25 mg capsules: white size 0 capsules marked “25 mg REV”.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

4.1.1 Multiple Myeloma (MM)

Revlimid is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.

Revlimid is indicated for the maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

4.1.2 Myelodysplastic Syndromes (MDS)

Revlimid is indicated for treatment of 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.

4.1.3 Mantle Cell Lymphoma (MCL)

Revlimid is indicated for the treatment of patients with relapsed and/or refractory mantle cell lymphoma.

4.2 Dose and Method of Administration

Treatment must be initiated and monitored under the supervision of a registered Specialist Physician experienced in the management of haematological and oncological malignancies.

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 and either one hour before or two hours after food.

If less than 12 hours have elapsed since missing a dose, the patient can take the dose. If more than 12 hours have 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.

4.2.1 Dosage

4.2.1.1 Multiple Myeloma

4.2.1.1.1 Newly Diagnosed Multiple Myeloma (NDMM) in Patients Not Eligible for autologous stem cell transplantation (ASCT)

For NDMM patients, CBC should be assessed every 7 days (weekly) for the first 2 cycles, every 2 weeks (Days 1 and 15) of cycle 3, and every 28 days (4 weeks) thereafter.

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 low-dose dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of repeated 28-day cycles. Patients should continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings.

For elderly patients (i.e. > 75 years of age) with NDMM treated with len/dex, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Lenalidomide treatment in combination with dexamethasone must not be started if the Absolute Neutrophil Count (ANC) < 1.5 x 10^9/L, and platelet count < 50 x 10^9/L.

Recommended dose adjustments for NDMM patients not eligible for ASCT receiving len/dex are found in Section 4.2.2 (Dose Adjustments).

4.2.1.1.2 Newly Diagnosed Multiple Myeloma (NDMM) in Patients Post autologous stem cell transplantation (ASCT)

Lenalidomide maintenance therapy should be initiated after adequate haematologic recovery following ASCT. The recommended starting dose of lenalidomide is 10 mg orally once daily continuously. After 3 months of maintenance therapy, the dose can be increased to 15 mg/day if tolerated. Patients should continue lenalidomide therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings.

Lenalidomide treatment must not be started if the ANC is < 1 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose adjustments for NDMM post-ASCT patients receiving lenalidomide maintenance are found in Section 4.2.2 (Dose Adjustments).
.

4.2.1.1.3 Previously Treated Multiple Myeloma (MM)

For patients with previously treated MM, CBC (including white blood cell count with differential count, platelet count), haemoglobin, and haematocrit should be performed at baseline, every 2 weeks for the first 12 weeks of lenalidomide treatment, and monthly thereafter to monitor for cytopenias.

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. Treatment should be continued until disease progression or unacceptable toxicity. Dosing is continued or modified based upon clinical and laboratory findings.

Lenalidomide treatment must not be started if the 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 for previously treated MM patients are found in Section 4.2.2 (Dose Adjustments).

4.2.1.2 Myelodysplastic Syndromes (MDS)

For patients on therapy for del 5q MDS, CBC should be monitored weekly for the first 8 weeks of therapy and at least monthly thereafter.

The recommended starting dose of lenalidomide is 10 mg given orally once a day on Days 1 to 21 of repeating 28-day treatment cycles. Dosing is continued or modified based upon clinical and laboratory findings.

Lenalidomide treatment must not be started if the ANC < 0.5 x 10^9/L, and/or platelet counts < 50 x 10^9/L.

Recommended dose adjustments for MDS patients are found in Section 4.2.2 (Dose Adjustments).

4.2.1.3 Previously Treated Mantle Cell Lymphoma (MCL)

For MCL patients treated with lenalidomide, CBC monitoring is recommended weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then at the start of each cycle thereafter.

The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1-21 of repeating 28-day cycles. Treatment should be continued until disease progression or unacceptable toxicity. Dosing is continued or modified based upon clinical and laboratory findings.

Recommended dose adjustments for MCL patients are found in Section 4.2.2 (Dose Adjustments).

4.2.2 Dose Adjustments

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

4.2.2.1 Thrombocytopenia and/or Neutropenia

4.2.2.1.1 Multiple Myeloma

Newly Diagnosed Multiple Myeloma (NDMM) in Patients Not Eligible for ASCT

- *Dose Reduction Levels*

	Lenalidomide	Dexamethasone
Starting dose	25 mg	40 mg
Dose Level 1	20 mg	20 mg
Dose Level 2	15 mg	12 mg
Dose Level 3	10 mg	8 mg
Dose Level 4	5 mg	4 mg
Dose Level 5	2.5 mg	Not applicable

- *Dose Reduction Guidance*

Thrombocytopenia	
When platelets:	**Recommended Lenalidomide Course**
First fall to < 25 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing is resumed at next cycle. Do not dose below 2.5 mg daily

Neutropenia[b]	
When neutrophils:	**Recommended Lenalidomide Course**
First fall to < 0.5 x 10^9/L or < 1.0 x 10^9/L associated with fever (temperature ≥ 38.5°C)	Interrupt lenalidomide treatment
Return to 1.0 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting Dose
Return to ≥ 0.5 x 10^9/l when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume at next lower dose level once daily. Do not dose below 2.5 mg daily

a: If dose-limiting toxicity occurs on > Day 15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

b: At the physician's discretion, if neutropenia is the only toxicity at any dose level, treat the patient with granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

If the dose of lenalidomide was reduced for a haematologic dose-limiting toxicity (DLT), the dose of lenalidomide may be re-increased to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued len/dex therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC $\geq 1.5 \times 10^9$/L with a platelet count $\geq 100 \times 10^9$/L at the beginning of a new cycle at the current dose level).

Newly Diagnosed Multiple Myeloma (NDMM) in Patients Post-ASCT

- *Dose Reduction Levels*

	Starting dose (10 mg)	**If dose increased (15 mg)***
Dose Level 1	5 mg	10 mg
Dose Level 2	5 mg (Days 1-21 of 28-day cycle)	5 mg
Dose Level 3	Not applicable	5 mg (Days 1-21 of 28-day cycle)
	Do not dose below 5 mg (Days 1-21 of 28-day cycle)	

* After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg if tolerated

- *Dose Reduction Guidance*

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 once daily
For each subsequent drop below 30×10^9/L	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9$/L	Resume lenalidomide at next lower dose level once daily

Neutropenia[a]	
When neutrophils:	**Recommended Course**
First fall to $< 0.5 \times 10^9$/L	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9$/L	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below 0.5×10^9/L	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9$/L	Resume lenalidomide at next lower dose level once daily

a: At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide.

Previously Treated Multiple Myeloma (MM)

- *Dose Reduction Levels*

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

- *Dose Reduction Guidance*

Thrombocytopenia	
When platelets:	**Recommended Course**
First fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at Dose Level 1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume at next lower dose level once daily.

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

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

4.2.2.1.2 Myelodysplastic Syndromes (MDS)

- *Dose Reduction Guidance*

For patients with MDS, dose reduction guidelines are divided into 2 sets - for within the first 4 weeks of treatment, and after the first 4 weeks of treatment.

i). For patients who experience thrombocytopenia or neutropenia <u>within the first 4 weeks</u> of treatment:

Thrombocytopenia		
When baseline:	**When platelets:**	**Recommended Course**
Platelet count ≥ 100 x 10^9/L	Fall to < 50 x 10^9/L	Interrupt lenalidomide treatment
	Return to ≥ 50 x 10^9/L	Resume lenalidomide at 5 mg/day
Platelet count ≥ 60 x 10^9 and < 100 x 10^9/L	Fall by 50% of the baseline value	Interrupt lenalidomide treatment
	Return to ≥ 50 x 10^9/L	Resume lenalidomide at 5 mg/day
Platelet count < 60 x 10^9/L	Fall by 50% of the baseline value	Interrupt lenalidomide treatment
	Return to ≥ 30 x 10^9/L	Resume lenalidomide at 5 mg/day

Neutropenia		
When baseline:	**When neutrophils:**	**Recommended Course**
ANC ≥ 1 x 10^9/L	Fall to < 0.75 x 10^9/L	Interrupt lenalidomide treatment
	Return to ≥ 1 x 10^9/L	Resume lenalidomide at 5 mg/day
ANC < 1 x 10^9/L	Fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
	Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at 5 mg/day

ii). For patients who experience thrombocytopenia or neutropenia after the first 4 weeks of treatment:

Thrombocytopenia	
During treatment at 10 mg/day:	
When platelets:	**Recommended Course**
Fall to < 30 x 10^9/L or < 50 x 10^9/L with platelet transfusions	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L (without haemostatic failure)	Resume lenalidomide at 5 mg/day

During treatment at 5 mg/day:	
Fall to < 30 x 10^9/L or < 50 x 10^9/L with platelet transfusions	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L (without haemostatic failure)	Resume lenalidomide at 5 mg/day every other day

Neutropenia	
During treatment at 10 mg/day:	
When neutrophils:	**Recommended Course**
Fall to < 0.5 x 10^9/L for ≥ 7 days or to < 0.5 x 10^9/L associated with fever (temperature ≥ 38.5°C)	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at 5 mg/day

During treatment at 5 mg/day:	
Fall to < 0.5 x 10^9/L for ≥ 7 days or to < 0.5 x 10^9/L associated with fever (temperature ≥ 38.5°C)	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at 5 mg every other day

4.2.2.1.3 Previously Treated Mantle Cell Lymphoma (MCL)

- *Dose Reduction Guidance*

Thrombocytopenia	
When platelets:	**Recommended Course**
First fall to < 50 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 60 x 10^9/L	Resume lenalidomide at 20 mg/day
For each subsequent drop below 50 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 60 x 10^9/L	Resume lenalidomide at 5 mg less than the previous dose once daily. After 5 mg daily dose, resume lenalidomide at 5 mg every other day. Do not dose below 5 mg every other day.

Neutropenia	
When neutrophils:	**Recommended Course**
First fall to < 1.0 x 10^9/L for at least 7 days OR Fall to < 1.0 x 10^9/L with associated fever (body temperature ≥ 38.5°C) OR Fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 1 x 10^9/L	Resume lenalidomide at 20 mg once daily
For each subsequent drop below < 1.0 x 10^9/L for at least 7 days or drop to < 1.0 x 10^9/L with associated fever (≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt lenalidomide treatment

Neutropenia	
When neutrophils:	**Recommended Course**
Return to $\geq 1.0 \times 10^9$/L	Resume lenalidomide at 5 mg lower than the previous dose. After 5 mg daily dose, resume lenalidomide at 5 mg every other day. Do not dose below 5 mg every other day.

4.2.2.2 Renal impairment

Lenalidomide is substantially excreted by the kidney. With patients with impaired renal function, care should be taken in dose selection. Monitoring of renal function is advised in patients with renal impairment.

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 severely impaired renal function, or end stage renal disease.

Renal Function (CLcr)	**Dose Adjustment**	
	Starting dose	**Starting dose**
Normal renal function / mild renal impairment ($\geq$ 60 mL/min)	25 mg once daily	10 mg once daily
Moderate renal impairment (30 $\leq$ CLcr < 60 mL/min)	10 mg once daily*	5 mg once daily
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	15 mg every other day	5 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	5 mg, 3 times a week following each dialysis

CLcr = creatinine clearance.

* 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.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification should be based on individual patient treatment tolerance. Monitoring of patients with impaired renal function for signs and symptoms of neutropenia or thrombocytopenia should be done as per the recommendations in Section 4.4. (Special warnings and Precautions for Use).

4.2.2.3 Hepatic impairment

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

4.2.2.4 Thromboembolism

If a 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.

4.2.2.5 Tumour Flare Reaction (TFR)

In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to $\leq$ Grade 1. Patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

4.2.2.6 Dermatological Reactions

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

4.2.2.7 Hepatic Disorders

If abnormal liver function test results are reported, treatment with lenalidomide should be interrupted. Once parameters have returned to baseline, treatment at a lower dose may be considered.

4.2.2.8 Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to lenalidomide, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2, at the physician's discretion.

4.3 Contraindications

- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the *i-access*® Program are met (see Section 4.4.1. [Pregnancy Warning]).
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for Use

4.4.1 Pregnancy Warning

If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, the conditions of the *i-access*® Program must be fulfilled for all patients.

4.4.1.1 The *i-access*® Program Conditions for Pregnancy Prevention

Revlimid is available under a restricted distribution program (*i-access*®). Only physicians and pharmacists registered with this Program can prescribe and dispense the product. In addition, Revlimid must only be dispensed to patients who are registered and meet all the conditions of the Program.

4.4.1.1.1 Females 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.

Female patients of non-childbearing potential are only required to comply with the General Conditions listed within the *i-access*® Program (see Section 4.4.1.1.5).

4.4.1.1.2 Females of Childbearing Potential

Female patients of childbearing potential must comply with the following requirements on counselling, contraception and pregnancy testing.

If pregnancy occurs in a female patient 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. Similarly, if pregnancy occurs in a partner of a male patient taking lenalidomide, the female

partner should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Counselling

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

- She understands the potential teratogenic risk to the unborn child.
- She understands and agrees to comply with 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 female 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 her physician 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 medically supervised pregnancy testing every 4 weeks.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

Contraception

Female patients of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy, 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.

Table 1. Recommended Methods of Contraception

Contraceptive method	Comments
Contraceptive implant Levonorgestrel-releasing intrauterine system (IUS)	Contraceptive 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.
Medroxyprogesterone acetate depot	
Tubal ligation	
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 MM patients taking len/dex, and to a lesser extent in patients with MM, MDS or MCL taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, the patient should switch to one of the effective methods

	listed in this table. 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.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential as outlined below.

This requirement includes females of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. For females of childbearing potential, dispensing of lenalidomide must occur within a maximum of 7 days of the negative pregnancy test.

- *Prior to Starting Treatment*

A medically supervised pregnancy test should be performed when lenalidomide is prescribed. The test should occur either at the time of consultation, or in the 3 days prior to the visit to the prescriber and at a point where the patient has been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide. This requirement includes females of childbearing potential who practice absolute and continuous abstinence.

- *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. 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. This requirement includes females of childbearing potential who practice absolute and continuous abstinence.

4.4.1.1.3 Male Patients

Male patients must comply with the following requirements on counselling and contraception as clinical data has demonstrated the presence of lenalidomide in human semen.

Counselling and contraception

- He understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential.
- He understands and complies with the need for the use of a condom (if engaged in sexual activity with a female of childbearing potential) throughout treatment duration, during dose interruption, and for 1 week after cessation of treatment if his partner is of childbearing potential and has no contraception.
- He understands that if his partner becomes pregnant whilst he is taking lenalidomide or during the 1st week after he discontinues taking lenalidomide, he should inform his treating physician immediately.
- He understands that he must not donate sperm during therapy (including during dose interruptions) or for 1 week following discontinuation of lenalidomide.

4.4.1.1.4 Prescribers

- Ensure that female patients of childbearing potential comply with the conditions of the *i-access*® Program, including confirmation that the patients have an adequate level of understanding of the Program requirements.
- Provide full patient information about the potential teratogenic risk and the strict pregnancy prevention measures as specified in the *i-access*® Program to female patients of childbearing potential and, as appropriate, to male patients.

- Ensure that all patients acknowledge and agreed to comply with the aforementioned conditions of the *i-access*® Program.

4.4.1.1.5 General conditions

All 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.
All patients should not donate blood during therapy (including during dose interruptions), or for 1 week following discontinuation of lenalidomide. In Australia, patients with a history of cancers that involve the haematopoietic system directly e.g. myeloma and lymphoma, are permanently excluded from donating blood.

4.4.2 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 minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

4.4.3 Venous and Arterial Thromboembolism

In patients with MM, the combination of len/dex is associated with an increased risk of venous thromboembolism [VTE (predominantly DVT and PE)].

In patients with MM, MDS or MCL, treatment with lenalidomide monotherapy was associated with a lower risk of VTE (predominantly DVT and PE) than in MM patients treated with lenalidomide in combination therapy.

In patients with MM, the combination of len/dex is associated with an increased risk of arterial thromboembolism [ATE (predominantly myocardial infarction and cerebrovascular event)]. The risk of ATE is lower in MM patients treated with lenalidomide monotherapy than in MM patients treated with lenalidomide in combination therapy.

Patients with known risk factors for thromboembolism (including prior thrombosis) should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). 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 MM patients receiving len/dex. A haemoglobin concentration above 120 g/L 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.

If a 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, 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.

4.4.4 Neutropenia and Thrombocytopenia

The major dose-limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. Patients with neutropenia should be monitored for signs of infection. Patients should be advised to promptly report febrile episodes. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxis, especially with use of concomitant medication that may increase risk of bleeding. Therefore, co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution. Appropriate management should be instituted if such toxicity is observed. Patients taking Revlimid should have their complete blood counts (CBC) assessed periodically as described below. A dose interruption and/or dose reduction may be required.

4.4.4.1 Newly Diagnosed Multiple Myeloma (NDMM)

For NDMM patients, CBC should be assessed every 7 days (weekly) for the first 2 cycles, every 2 weeks (Days 1 and 15) of cycle 3, and every 28 days (4 weeks) thereafter.

4.4.4.2 Previously Treated Multiple Myeloma (MM)

The combination of len/dex in previously treated MM patients is associated with a higher incidence of Grade 4 neutropenia (4.8% in len/dex-treated patients compared with 0.6% in placebo/dex-treated patients. Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in len/dex-treated patients compared to 0.0% in placebo/dex-treated patients; see Section 4.8. [Adverse Effects]). A dose reduction may be required. In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of len/dex in previously treated MM patients is associated with a higher incidence of Grade 3 and Grade 4 thrombocytopenia (10.8% and 1.4%, respectively, in len/dex-treated patients compared to 5.4% and 0.9% in placebo/dex-treated patients; see Section 4.8. [Adverse Effects]).

For patients with previously treated MM, CBC (including white blood cell count with differential count), platelet count, haemoglobin, and haematocrit should be performed at baseline, every 2 weeks for the first 12 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.

4.4.4.3 Myelodysplastic Syndromes (MDS)

In clinical studies of patients with del 5q MDS, lenalidomide as monotherapy was associated with significant neutropenia and thrombocytopenia. Grade 3 or 4 haematologic toxicity was seen in 80% of patients. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days).

Patients on therapy for del 5q MDS should have their CBC monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require the use of blood product support and/or growth factors.

4.4.4.4 Previously Treated Mantle Cell Lymphoma (MCL)

For MCL patients treated with lenalidomide, CBC monitoring is recommended weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then at the start of each cycle thereafter. A dose interruption and/or dose reduction may be required.

4.4.5 Peripheral Neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long-term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

4.4.6 Tumour Lysis Syndrome and Tumour Flare Reaction

4.4.6.1 Multiple Myeloma (MM) and Myelodysplastic Syndromes (MDS)

There have been rare reports of tumour lysis syndrome (TLS) in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.

4.4.6.2 Lymphomas, including Previously Treated Mantle Cell Lymphoma (MCL)

TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukaemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. Patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken.

There were no reports of TLS in Study MCL-001. In Study MCL-002, TLS was reported for one patient in each treatment arm.

In Study MCL-001, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. In Study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2.

Careful monitoring and evaluation for TFR is recommended. Tumour flare may mimic progression of disease. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients in Studies MCL-001 and MCL-002 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

4.4.7 Allergic Reactions and Serious Skin Reactions

Rare cases of angioedema and serious dermatological reactions including Stevens-Johnson syndrome toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported from post-marketing experience. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events have the potential to be fatal.

Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash. Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome, toxic epidermal necrolysis or DRESS is suspected. Revlimid should not be resumed following the discontinuation for these reactions.

4.4.8 Atrial Fibrillation

In the two pivotal randomised controlled trials in previously treated (relapsed/refractory) MM patients, atrial fibrillation occurred in 14 (4.0%) subjects treated with len/dex compared to 4 (1.1%) subjects treated with placebo/dex (unadjusted for the longer on-study observation time for patients receiving lenalidomide). Careful review of these cases revealed the presence of multiple risk factors for atrial fibrillation (e.g. infections, hypertension, congestive heart failure, electrolyte imbalance), and a causal relationship to lenalidomide treatment has not yet been determined.

4.4.9 Use in Patients with Impaired Thyroid Function

Cases of hypothyroidism and hyperthyroidism have been reported. Optimal control of co-morbid conditions that can affect thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

4.4.10 Use in Patients with 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 Revlimid.

4.4.11 Use in Hepatic impairment

Hepatic failure, including fatal cases, has been reported in patients treated with len/dex. This includes reports of acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis. 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 have been commonly reported and were generally asymptomatic and reversible upon dosing interruption. If abnormal liver function test results are reported, treatment with lenalidomide should be interrupted. Once parameters have returned to baseline, treatment at a lower dose may be considered.

4.4.12 Use in Renal impairment

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.

4.4.13 Use in the Elderly

Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and show that age does not influence the disposition of lenalidomide. No dose adjustments are needed for lenalidomide.

For NDMM patients > 75 years of age and not eligible for ASCT, a reduced starting dose of dexamethasone is recommended.

Lenalidomide has been used in clinical trials in previously treated MM patients up to 86 years of age. The percentage of patients aged 65 or over was not significantly different between the len/dex and placebo/dex groups. No overall difference in effectiveness was observed between these patients and younger patients. However, overall serious adverse events (AEs), in particular the serious vascular events (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) and serious cardiovascular events (including atrial fibrillation), were all more frequent in lenalidomide-treated patients 65 years and over.

Lenalidomide has also been used in MDS clinical trials in patients up to 95 years of age. Of the 395 patients in the MDS clinical trials who received 10 mg lenalidomide, 72.2% were aged 65 and over. No overall difference in safety was observed between these patients and younger patients, but greater pre-disposition of older individuals to drug-related toxicities cannot be ruled out.

Lenalidomide is known to be substantially excreted by the kidney. The risk of ADRs may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased renal function, so care should be taken in dose selection for such patients. Renal function should therefore be monitored.

4.4.14 Paediatric Use

There is no experience in treating children and adolescents with Revlimid. Therefore, lenalidomide should not be used in the paediatric age group (0-18 years).

4.4.15 Second Primary Malignancies (SPM)

In clinical trials in NDMM patients not eligible for ASCT, a 4.9-fold increase in incidence rate of haematologic second primary malignancies (SPM) (cases of AML and MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone (MPR+R) until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (MPp+p) (0.36 per 100 person-years). A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving MPR+R (9 cycles) (1.57 per 100 person-years) compared with MPp+p (0.74 per 100 person-years).

In NDMM patients receiving lenalidomide in combination with dexamethasone (len/dex) until progression or for 18 months, the haematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (MPT) (0.79 per 100 person-years). A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving len/dex until progression or for 18 months (1.58 per 100 person-years) compared to MPT (1.19 per 100 person-years).

In clinical trials of NDMM patients eligible for ASCT, an increased incidence rate of haematologic SPM (most notably AML, MDS and B-cell malignancies [including Hodgkin's lymphoma] has been observed in patients receiving lenalidomide maintenance immediately following high-dose melphalan/ASCT (1.31 per 100 person-years) compared with patients who received placebo (0.58 per 100 person-years). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms.

Based on a low number of cases, a numerical imbalance in SPM (comprising mainly of basal cell and squamous cell skin cancers) has been observed in clinical trials in previously treated MM patients with len/dex (3.98 per 100 patient-years) compared with placebo/dex (1.38 per 100 patient-years).

Subjects who received lenalidomide-containing therapy until disease progression did not show a higher incidence of invasive SPM than subjects treated in the fixed duration lenalidomide-containing arms. These results suggest that duration of lenalidomide treatment is not associated with an increased risk for the occurrence of invasive SPM.

Both the benefit achieved with Revlimid and the risk of SPMs should be considered and discussed with patients, before initiating treatment with the product. Physicians should also carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPMs and institute treatment as appropriate.

4.4.16 Increased Mortality in Chronic Lymphocytic Leukaemia (CLL)

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with CLL, single agent Revlimid therapy was associated with an increased risk of death as compared to single agent chlorambucil. Lenalidomide is not recommended for use in CLL outside of controlled clinical trials.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in MM patients receiving len/dex.

In vitro, lenalidomide does not inhibit UGT1A1-mediated bilirubin glucuronidation in human liver microsomes derived from donors representing genotypes UGT1A1*1/*1, UGT1A1*1/*28, and UGT1A1*28/*28.

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.

4.5.1 Oral Contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer (see below). 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.

Lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes *in vitro*. Hence, co-administration of cytochrome P450 substrates (including hormonal contraceptives), inhibitors or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions.

However, it is noteworthy that there is an increased risk of VTE in patients treated with lenalidomide in combination with dexamethasone for MM and to a lesser extent in patients treated with lenalidomide monotherapy for MM, MDS or MCL. Since there is an increased risk of VTE in patients taking combined oral contraceptive pills or hormone replacement therapy, physicians should discuss the benefit/risk of contraceptive methods or hormone replacement with their patients. Effective measures to avoid pregnancy must be taken.

4.5.2 Dexamethasone

In patients with MM, co-administration of single or multiple doses of dexamethasone (40 mg/day) had no significant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg/day).

4.5.3 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.

4.5.4 Digoxin

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% [90% CI: 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. In the same study, the co-administration of digoxin (a P-glycoprotein substrate) did not significantly affect the pharmacokinetics of lenalidomide.

4.5.5 Human Efflux Transporters

Lenalidomide is a weak substrate but not an inhibitor of P-glycoprotein (P-gp). Co-administration of multiple doses of P-gp inhibitor, quinidine (600 mg, twice daily) had no effect on the single dose pharmacokinetics of lenalidomide (25 mg). Single dose co-administration of lenalidomide (25 mg) and P-gp inhibitor/substrate, temsirolimus (25 mg), does not affect the pharmacokinetics of either drug.

Lenalidomide is not an inhibitor of bile salt export pump (BSEP), MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2.

4.5.6 Renal Drug Interactions

Renal drug-drug interaction studies have not been performed. The renal clearance of lenalidomide is slightly greater than the glomerular filtration rate, suggesting that active secretion contributes to a minor

extent (≤ 25%) of renal clearance. Hence, the inhibition of the active secretion of lenalidomide will most likely not result in a clinically relevant drug-drug interaction.

4.6 Fertility, Pregnancy and Lactation

4.6.1 Effects on Fertility

A fertility and early embryonic development study in male and female rats, with administration of lenalidomide up to 500 mg/kg/day, produced no parental toxicity and no adverse effects on fertility or early embryonic development. The systemic exposure in rats at 500 mg/kg was > 70-fold higher than the human exposure at 25 mg/day, based on AUC.

4.6.2 Use in Pregnancy (Pregnancy Category X) (see section 4.4.1)

For lenalidomide, no clinical data on exposed pregnancies are available. Because lenalidomide is a structural analogue of thalidomide (a known human teratogen that causes severe, life-threatening birth defects), and has shown teratogenic effects in animal studies, lenalidomide must not be used in pregnant women. Females of childbearing potential must use effective means of contraception.

Embryofoetal development studies were conducted in monkeys and rabbits. In monkeys, lenalidomide was teratogenic at systemic exposures (based on plasma AUC) well below that anticipated clinically, and a NOEL for the teratogenic effects could not be established in the study.

In rabbits treated with 3, 10 and 20 mg/kg/day orally, maternal and developmental toxicity was noted at ≥ 10 mg/kg/day. The toxicity was characterised by slightly reduced foetal body weights, increased incidences of post-implantation loss, and gross external findings in the foetuses associated with maternal toxicity of lenalidomide. Increased incidences of soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day. The NOEL for developmental toxicity of lenalidomide in rabbits was identified as 3 mg/kg/day, which is associated with a plasma AUC value equivalent to that anticipated clinically at the 25 mg/day dose in humans.

4.6.3 Use in Lactation

It is not known whether lenalidomide is excreted in human milk. Because of the potential for adverse drug reactions (ADRs) in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother.

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, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Adverse Effects (Undesirable Effects)

4.8.1 Tabulated Summary of Adverse Events

4.8.1.1 Multiple Myeloma (MM)

4.8.1.1.1 Newly Diagnosed Multiple Myeloma (NDMM) in Patients Not Eligible for ASCT

In the large phase III, controlled study (MM-020), data were evaluated from 1072 patients who received at least one dose of Revlimid with low-dose dexamethasone, either given Continuously (Rd) or for 18 cycles (Rd18). Median treatment duration was notably longer in the Continuous Rd arm (80.1 weeks) when compared to the Rd18 arm (72 weeks) and the MPT arm (67.1 weeks), as the Continuous Rd arm sustained treatment until disease progression, while treatments in arms Rd18 and MPT were both capped

at 72 weeks. The median average daily dose of lenalidomide was 21.8 mg in the Continuous Rd arm and 24.4 mg in the Rd18 arm.

In general, the most frequently reported adverse events (AEs) were comparable in Arm Rd until progression and Arm Rd18, and included diarrhoea, anaemia, constipation, peripheral oedema, neutropenia, fatigue, back pain, nausea, asthenia, insomnia, decreased appetite and muscle spasms. The most frequently reported Grade 3 or 4 events included neutropenia, anaemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalaemia, rash, cataract, lymphopenia, dyspnoea, DVT, hyperglycaemia, and leukopenia. No particular AE led to discontinuation of any study drug in more than 2% of subjects in either arm. Over time, the Rd regimen was generally better tolerated than MPT. Subjects in Arm MPT discontinued treatment sooner and more frequently prior to disease progression than subjects receiving Rd. Subjects in Arm MPT also more frequently experienced AEs leading to study drug discontinuation. Extended treatment in the Rd arm beyond 18 months generally resulted in a limited increase in most AEs compared with Rd18 or MPT.

For the Rd regimen, 66.4% of patients experienced at least one AE leading to Revlimid interruption, 60.0% experienced at least one AE leading to dexamethasone interruption, and 69.2% experienced at least one AE leading to Revlimid or dexamethasone interruption, compared to 77.4% in the MPT arm for thalidomide or melphalan or prednisone interruption.

A list of the treatment-emergent adverse events (TEAEs) that occurred at a frequency of greater than or equal to 10% in any arm for Study MM-020 is provided in Table 3 (see section 4.8.1.1.3).

4.8.1.1.2 Newly Diagnosed Multiple Myeloma (NDMM) in Patients Post-ASCT

The safety of lenalidomide was assessed in two Phase III multicenter, randomised, double-blind, 2- arm, parallel group, placebo-controlled studies: CALGB 100104 and IFM 2005-02. The AEs from Study CALGB 100104 included events reported post-high dose melphalan/ASCT as well as events from the maintenance treatment period. In Study IFM 2005-02, the AEs were from the maintenance treatment period only.

In Study CALGB 100104, the overall frequencies of TEAEs, Grade 3 or 4 TEAEs, serious TEAEs (SAEs), and TEAEs leading to discontinuation of study drug were higher in the subjects administered lenalidomide (96.0%, 79.5%, 28.1%, and 28.1%, respectively) compared to subjects administered placebo (85.1%, 55.2%, 12.2%, and 2.7%, respectively). Of note, the treatment duration in the CALGB lenalidomide arm was longer than in the CALGB placebo arm (mean maintenance treatment duration: 30.3 months versus 13.2 months, respectively; total person-years of maintenance therapy: 565 versus 243, respectively), resulting in a longer AE observation period in the lenalidomide arm compared with the placebo arm.

In Study IFM 2005-02, the frequency of overall TEAEs in subjects administered lenalidomide (99.3%) was similar compared to placebo subjects (97.1%). For Grade 3 or 4 TEAEs, SAEs, and TEAEs leading to discontinuation of study drug, the overall frequencies of AEs were higher in the lenalidomide arm (75.1%, 44.7%, and 27.6%, respectively) compared with the placebo arm (32.1%, 22.9%, and 10.0%, respectively).

A list of the TEAEs that occurred at a frequency of greater than or equal to 10% in any arm for Studies CALGB 100104 (post-transplant and maintenance period) and IFM 2005-02 (maintenance period only) is provided in Table 2 below.

Table 2. Most frequently reported Treatment-Emergent Adverse Events (≥ 10% in Lenalidomide Arm) in Studies CALGB 100104 (post-transplant and maintenance period) and/or IFM 2005-02 (maintenance period only)

System organ class Preferred term	% frequency			
	CALGB 100104		IFM 2005-02	
	Len	Pbo	Len	Pbo
Number of patients (N)	**224**	**221**	**293**	**280**
Infections and Infestations				
Bronchitis	4.5	4.1	47.4	37.1
Nasopharyngitis	2.2	0.9	34.8	30.0
Upper respiratory tract infection	26.8	15.8	10.9	6.4
Gastroenteritis	0.0	0.0	22.5	19.6
Neutropenic infection	17.9	8.6	0.0	0.0
Rhinitis	0.9	0.0	15.0	6.8
Sinusitis	3.6	1.4	14.0	9.3
Influenza	3.6	2.3	13.3	6.8
Blood and Lymphatic System Disorders				
Neutropenia	79.0	42.5	60.8	11.8
Thrombocytopenia	72.3	45.7	23.5	10.4
Leukopenia	22.8	11.3	31.7	7.5
Anaemia	21.0	12.2	8.9	5.4
Lymphopenia	17.9	13.1	4.4	1.1
Febrile neutropenia	17.4	15.4	2.4	0.4
Nervous system disorders				
Paraesthesia	0.9	0.0	13.3	10.7
Peripheral sensory neuropathy	12.1	11.8	-	-
Respiratory, thoracic and mediastinal disorders				
Cough	10.3	5.4	27.3	20.0
Lung disorder	0.4	0.0	11.6	3.6
Gastrointestinal Disorders				
Diarrhoea	54.5	37.6	38.9	12.1
Nausea	14.7	10.0	10.6	10.0
Constipation	5.4	3.6	12.6	8.9
Gastrointestinal disorder	0.9	0.9	12.3	2.9
Abdominal pain	3.6	3.2	10.6	5.4
Hepatobiliary Disorders				
Hyperbilirubinaemia	15.2	8.6	1.4	0.4
Skin and Subcutaneous Tissue Disorders				
Rash	31.7	21.7	7.5	6.1
Dry skin	4.0	1.8	10.6	7.5
Metabolism and Nutrition Disorders				
Hypokalaemia	10.7	5.9	4.1	0.4
Musculoskeletal and connective tissue disorders				
Muscle spasms	0.0	0.5*	33.4	15.4
Back pain	7.6	11.3*	25.9	28.2*
Arthralgia	4.9	6.3*	14.0	16.8*
General Disorders and Administration Site Conditions				
Asthenia	0.0	0.5*	29.7	18.9
Fatigue	22.8	13.6	10.6	5.4
Pyrexia	7.6	4.5	20.5	9.3
Pain	1.3	1.8*	10.6	11.8*

Len = lenalidomide; Pbo = placebo
* Events where frequency in the placebo arm was the same or higher than the lenalidomide arm(s) in the same study
- Term not reported.

The following SAEs were also noted in both studies - lung infection, infection, urinary tract infection, herpes zoster and myelodysplastic syndrome.

4.8.1.1.3 Previously Treated Multiple Myeloma (MM)

In two Phase III placebo-controlled studies (MM-009 and MM-010), 353 patients with previously treated MM were exposed to the len/dex combination and 351 to the placebo/dex combination. The median duration of exposure to study treatment was significantly longer (44.0 weeks) in the len/dex group as compared to placebo/dex (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 len/dex (39.7%) than in placebo/dex patients (70.4%).

The most serious AEs were: Venous thromboembolism (DVT and PE) and Grade 4 neutropenia (see Section 4.4. [Special Warnings and Precautions for Use]).

Table 3 collectively shows the TEAEs that occurred at a frequency of ≥ 10% in any of the len/dex study arms for studies in subjects with previously treated MM (Studies MM-009 and MM-010) and the study in NDMM subjects not eligible for ASCT (Study MM-020).

Table 3. Treatment-Emergent Adverse Events Reported for at least 10% of Subjects in Any Lenalidomide Arm – Previously treated MM Studies (MM-009/010), and ASCT Non-Eligible NDMM Study (MM-020)

System Organ Class Preferred term	% frequency				
	MM-009/010		MM-020		
	RD	Pbo	Continuous[a] Rd	Rd18[b]	MPT
Number of patients (N)	**353**	**350**	**532**	**540**	**541**
Blood and Lymphatic System Disorders					
Anaemia	36.0	25.1	43.8	35.7	42.3
Neutropenia	44.8	8.3	35.0	33.0	60.6*
Thrombocytopenia	22.9	12.0	19.5	18.5	25.0*
Leukopenia	9.9	4.0	11.8	11.1	17.4*
Lymphopenia	5.9	2.6	11.1	8.0	13.1*
Eye disorders					
Cataract	8.2	2.9	13.7	5.7	0.9
Vision blurred	18.4	12.3	5.5	3.7	4.4
Gastrointestinal Disorders					
Diarrhoea	45.3	29.7	45.5	38.5	16.5
Constipation	41.9	21.7	43.0	39.3	52.7*
Nausea	27.8	21.7	28.6	23.7	30.5*
Vomiting	13.3	9.7	17.5	12.6	20.1*
Abdominal pain	11.0	6.6	13.0	7.6	5.5
Dyspepsia	17.0	14.6	10.7	5.2	6.7
General Disorders and Administration Site Conditions					
Oedema peripheral	32.3	24.9	39.7	31.3	39.7*
Fatigue	47.0	42.0	32.5	32.8	28.5
Asthenia	30.6	26.9	28.2	22.8	22.9
Pyrexia	29.5	24.0	21.4	18.9	14.0
Oedema	10.8	9.1	7.1	5.2	5.9
Infections and Infestations					
Bronchitis	16.1	9.1	16.9	10.9	7.9
Nasopharyngitis	22.1	9.7	15.0	10.0	6.1
Urinary tract infection	9.9	5.7	14.3	11.7	7.6
Upper respiratory tract infection	26.1	15.7	13.0	9.8	5.7
Pneumonia	16.7	8.6	12.4	12.6	7.4
Pharyngitis	16.7	9.7	1.3	1.5	1.5

System Organ Class Preferred term	% frequency				
	MM-009/010		MM-020		
	RD	Pbo	Continuous[a] Rd	Rd18[b]	MPT
Number of patients (N)	**353**	**350**	**532**	**540**	**541**
Investigations					
Weight decreased	19.8	15.4	13.5	14.4	8.9
Metabolism and Nutrition Disorders					
Decreased appetite	22.7	14.0	23.1	21.3	13.3
Hypokalaemia	15.9	6.6	17.1	11.5	7.0
Hyperglycaemia	16.7	14.3	11.7	9.6	3.5
Hypocalcaemia	9.9	3.1	10.7	10.4	5.7
Musculoskeletal and Connective Tissue Disorders					
Back pain	28.6	19.4	32.0	26.9	21.4
Muscle spasms	38.2	23.1	20.5	18.9	11.3
Arthralgia	20.7	18.3	19.0	13.1	12.2
Bone pain	17.0	11.7	16.4	14.3	11.5
Pain in extremity	15.9	11.1	14.8	12.2	11.3
Musculoskeletal pain	3.4	2.9	12.6	10.9	6.7
Musculoskeletal chest pain	8.8	6.9	11.3	9.4	7.2
Muscular weakness	16.7	16.3	8.1	6.5	5.4
Myalgia	11.3	11.1	5.1	3.5	3.1
Nervous System Disorders					
Peripheral sensory neuropathy	4.2	3.1	20.5	17.0	35.3*
Paraesthesia	15.0	13.4	16.0	13.7	19.0*
Dizziness	24.9	16.9	15.8	13.0	21.1*
Headache	27.2	25.4	14.1	9.6	10.4
Tremor	21.2	7.7	14.1	13.5	18.5*
Hypoaesthesia	11.6	7.7	8.3	4.4	7.6
Dysgeusia	15.3	10.0	7.3	8.3	4.1
Neuropathy peripheral	15.3	10.9	6.4	4.1	11.5*
Psychiatric Disorders					
Insomnia	38.0	37.7	27.6	23.5	9.8
Depression	13.6	10.9	10.9	8.5	5.5
Anxiety	12.5	9.7	7.7	6.7	7.6
Confusional state	10.8	6.9	7.1	5.4	4.6
Respiratory, Thoracic and Mediastinal Disorders					
Cough	26.9	25.4	22.7	17.4	12.6
Dyspnoea	25.8	18.0	22.0	16.5	20.9
Skin and Subcutaneous Tissue Disorders					
Rash	23.8	11.1	21.4	24.3	17.2
Hyperhidrosis	10.2	7.4	4.7	3.5	2.4
Vascular Disorders					
Deep vein thrombosis	9.3	4.6	10.2	6.7	3.7

MPT = melphalan, prednisone and thalidomide; Pbo = placebo; RD = lenalidomide + high-dose dexamethasone; Rd = lenalidomide + low-dose dexamethasone.

a = Continuous Rd arm where patients were dosed with lenalidomide + low-dose dexamethasone until progressive disease

b = Rd18 arm where patients were dosed with lenalidomide + low-dose dexamethasone for up to eighteen 28-day cycles (72 weeks)

* Events where frequency in the comparator MPT arm was the same or higher than the lenalidomide treatment arm(s) in Study MM-020.

4.8.1.2 Myelodysplastic Syndromes (MDS)

Data from the placebo-controlled MDS-004 study demonstrate that lenalidomide is also well tolerated in subjects with low- or intermediate-1-risk MDS with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities. The most frequently reported AEs were related to blood and lymphatic

system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

In study MDS-004, neutropenia in 76.8% (106/138) of subjects and thrombocytopenia in 46.4% (64/138) of subjects were the most frequently reported AEs. The next most common AEs observed were diarrhoea (34.8%), constipation (19.6%) and nausea (19.6%); pruritus (25.4%) and rash (18.1%); fatigue (18.1%) and oedema peripheral (15.2%); and muscle spasms (16.7%). Table 4 summarises the AEs that were reported in ≥ 10% of the Revlimid-treated patients in Study MDS-004.

Table 4: Most Frequently Reported (≥ 10% in lenalidomide arm) Adverse Events in Study MDS-004

System Organ Class Preferred term	% with Lenalidomide[a] (N=138)	% with Placebo (N=67)
General Disorders & Administration Site Conditions		
Fatigue	18.1	7.5
Oedema Peripheral	15.2	7.5
Pyrexia	13.8	6.0
Gastrointestinal Disorders		
Diarrhoea	34.8	17.9
Nausea	19.6	9.0
Constipation	19.6	7.5
Abdominal pain	10.9	6.0
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	16.7	9.0
Nervous System disorders		
Headache	14.5	9.0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	11.6	6.0
Infections and Infestations		
Nasopharyngitis	11.6	7.5
Bronchitis	11.6	4.5
Upper respiratory tract infection	10.9	6.0
Skin and Subcutaneous Tissue Disorders		
Pruritus	25.4	4.5
Rash	18.1	1.5
Dry Skin	10.1	1.5
Blood and Lymphatic System Disorders		
Neutropenia	76.8	17.9
Thrombocytopenia	46.4	3.0
Leukopenia	12.3	4.5

a: Combined 5 mg and 10 mg lenalidomide treatment arms from Study MDS-004.

The safety results (N=148) from the Phase II open-label study MDS-003 are consistent with the findings from MDS-004. Neutropenia (66.2%) and thrombocytopenia (64.9%) were the most frequently reported AEs, followed by diarrhoea (60.1%), pruritus (44.6%), fatigue (42.6%), rash (37.8%) and arthralgia (31.8%).

The most serious Grade 3 and Grade 4 AEs from the MDS-004 study (N=138, 5 mg and 10 mg doses combined) were neutropenia (5.8%), thrombocytopenia (5.8%), venous thromboembolism (DVT [3.6%] and PE [2.9%], and altered mood (0.7%). The frequency of these events in the open-label MDS-003 study (N=148) were neutropenia (64.9%), thrombocytopenia (54.7%) and venous thromboembolism (DVT [4.7%] and PE [3.4%]).

In the 10 mg group from study MDS-004, the dose of Revlimid was reduced or interrupted at least once due to an AE in 44 (62.3%) patients, which occurred a mean of 50.1 days into the study and lasted a mean of 26.8 days. Twenty-four (34.8%) subjects had a second dose reduction or interruption. In study MDS-003, the dose of Revlimid was reduced or interrupted at least once due to an AE in 127 (85.8%) patients, which occurred a mean of 75.2 days into the study and lasted a mean of 30.4 days. Eighty-two (55.4%) subjects had a second dose reduction or interruption. The mean interval between the first and second dose reduction/interruption was 198.2 days. The second dose reduction/interruption due to an AE lasted a mean of 44.5 days.

4.8.1.3 Previously Treated Mantle Cell Lymphoma (MCL)

The overall safety profile of Revlimid in patients with previously treated MCL is based on data from 254 patients from a Phase II, randomised, controlled study (MCL-002) and 134 patients from a Phase II, single arm study (MCL-001).

Table 5 summarises the most common AEs i.e. that were reported in ≥ 10% of the Revlimid-treated subjects in Studies MCL-001 and MCL-002.

Table 5: Most Frequently Reported (≥ 10% in lenalidomide arm) Adverse Events - Studies MCL-002 and MCL-001

System Organ Class Preferred term	MCL-002		MCL-001
	% with Lenalidomide (N=134)	% with Investigator's Choice (N=83)	% with Lenalidomide (N=134)
General Disorders & Administration Site Conditions			
Fatigue	21.0	4.8	33.6
Pyrexia	16.8	12.0	25.4
Asthenia	15.6	13.3	14.9
Oedema peripheral	10.2	10.8	16.4
Gastrointestinal Disorders			
Diarrhoea	22.8	9.6	34.3
Constipation	17.4	6.0	15.7
Nausea	10.8	14.5	31.3
Vomiting	6.0	10.8	12.7
Abdominal pain	9.6	4.8	10.4
Respiratory, Thoracic and Mediastinal Disorders			
Cough	11.4	4.8	30.6
Dyspnoea	7.2	8.4	20.1
Oropharyngeal pain	2.4	2.4	10.4
Infections and Infestations			
Nasopharyngitis	15.0	6.0	6.0
Upper respiratory tract infection	12.0	6.0	13.4
Pneumonia	6.6	4.8	10.4
Skin and Subcutaneous Tissue Disorders			
Rash	10.8	3.6	22.4
Pruritus	9.0	3.6	17.2
Blood and Lymphatic System Disorders			
Neutropenia	50.9	34.9	49.3
Thrombocytopenia	36.5	39.8	36.6
Anaemia	28.7	22.9	31.3
Leukopenia	16.8	21.7	14.9

Metabolism and Nutrition Disorders			
Decreased appetite	11.4	3.6	15.7
Hypokalaemia	8.4	1.2	13.4
Musculoskeletal and connective tissue disorders			
Back pain	9.0	0.0	14.9
Muscle spasms	7.8	3.6	12.7
Investigations			
Weight decreased	4.8	2.4	14.2

4.8.2 Tabulated List of Adverse Reactions {Multiple Myeloma (MM), Myelodysplastic Syndromes (MDS), and Mantle Cell Lymphoma (MCL)}

The ADRs observed in MM patients treated with len/dex or lenalidomide monotherapy post-ASCT, MDS patients treated with at least one dose of 10 mg lenalidomide, and in MCL patients are tabulated below by system organ class and frequency (Table 6). Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); and uncommon (≥ 1/1,000, < 1/100).

The following table is derived from data gathered during the main clinical trials in MM, MDS and MCL. The data were not adjusted according to differences in duration of treatment across the MM studies.

ADRs have been included under the appropriate category in the table below according to the highest frequency observed in the lenalidomide arm of any of the main clinical trials.

Table 6: Adverse Drug Reactions (including Grade 3 and 4 ADRs) observed in Patients in Main MM, MDS and MCL Studies*

Frequency	All ADRs	Grade 3 and 4 ADRs
Infections and Infestations		
Very common	Nasopharyngitis; Pharyngitis; Pneumonias; Bronchitis; Bacterial, viral and fungal infections (including opportunistic infections); Upper respiratory tract infection; Sinusitis	Bacterial, viral and fungal infections (including opportunistic infections); Pneumonia
Common	Sepsis	Bronchitis; Upper respiratory tract infection; Sepsis
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)		
Common	Tumour flare	Tumour flare; Squamous cell carcinoma of skin; Basal cell carcinoma
Blood and Lymphatic System Disorders		
Very common	Neutropenias; Thrombocytopenia; Anaemia; Leukopenias; Febrile neutropenia	Neutropenias; Thrombocytopenia; Anaemia; Leukopenias; Febrile neutropenia
Common	Pancytopenia	Pancytopenia
Immune System Disorders		
Uncommon	Hypersensitivity	
Endocrine Disorders		
Common	Hypothyroidism	
Metabolism and Nutrition Disorders		
Very common	Decreased appetite; Hyperglycaemia; Hypokalaemia; Hypocalcaemia	
Common	Hypomagnesaemia; Dehydration; Iron overload	Hypokalaemia; Hypocalcaemia; Hypophosphataemia; Diabetes mellitus; Hyperglycaemia; Dehydration; Hyponatraemia; Gout; Decreased appetite

Frequency	All ADRs	Grade 3 and 4 ADRs
Psychiatric Disorders		
Very common	Insomnia; Depression	
Common		Depression; Insomnia
Nervous System Disorders		
Very common	Peripheral neuropathies (excluding motor neuropathy); Dizziness; Tremor; Dysgeusia; Headache	
Common	Lethargy	Peripheral neuropathies (excluding motor neuropathy); Syncope; Dizziness; Cerebrovascular accident; Lethargy; Headache
Eye Disorders		
Very common	Cataracts; Blurred vision	
Common		Cataracts
Ear and Labyrinth Disorders		
Common	Vertigo	
Cardiac Disorders		
Common	Atrial fibrillation	Atrial fibrillation; Myocardial infarction (including acute); Cardiac failure (including congestive); Tachycardia
Vascular Disorders		
Very common	Venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism)	Venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism)
Common	Hypertension; Hypotension; Haematoma	Hypotension
Respiratory, Thoracic and Mediastinal Disorders		
Very common	Dyspnoea; Epistaxis; Cough	
Common		Dyspnoea; Respiratory distress; Pneumonitis
Gastrointestinal Disorders		
Very common	Diarrhoea; Constipation; Nausea; Abdominal pain; Dyspepsia; Vomiting	
Common	Abdominal pain upper; Dry mouth	Diarrhoea; Nausea; Abdominal pain; Constipation; Toothache; Vomiting
Hepatobiliary Disorders		
Very common	Abnormal liver function tests	
Common		Cholestasis; Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders		
Very common	Pruritus; Rash (including dermatitis allergic); Dry skin; Hyperhidrosis	
Common	Night sweats; Erythema	Rash; Pruritus
Musculoskeletal and Connective Tissue Disorders		
Very common	Musculoskeletal and connective tissue pain and discomfort; Muscle spasms; Arthralgia; Bone pain; Myalgia	
Common	Muscular weakness	Musculoskeletal and connective tissue pain and discomfort; Muscular weakness; Bone pain; Arthralgia
Renal and Urinary Disorders		
Very common	Renal failure (including acute)	
Common		Renal failure

Frequency	All ADRs	Grade 3 and 4 ADRs
General Disorders and Administration Site Conditions		
Very common	Pyrexia; Influenza-like illness syndrome (including pyrexia, cough, rhinitis, myalgia, musculoskeletal pain, headache and chills); Fatigue; Asthenia; Oedema (including peripheral)	
Common	Chest pain	Fatigue; Pyrexia; Asthenia
Investigations		
Very common	Weight decreased	
Common		Weight decreased
Injury, Poisoning and Procedural Complications		
Common	Fall; Contusion	Fall

* Algorithm applied for determination of ADRs from clinical trials and inclusion in table above, as follows:

- Controlled studies - MM-009, MM-010, MM-020, CALGB 100104, IFM 2005-02, MDS-004, and MCL-002
  - All treatment-emergent adverse events with ≥ 5.0% of subjects in the lenalidomide-containing arm(s) and ≥ 2.0% higher frequency (%) in lenalidomide-containing arm(s) compared to the non-lenalidomide arm
  - All treatment-emergent Grade 3 or 4 adverse events in ≥ 1.0% of subjects in lenalidomide-containing arm(s) and ≥ 1.0% higher frequency (%) in lenalidomide-containing arm(s) compared to the non-lenalidomide arm
- Uncontrolled MDS study - MDS-003
  - All treatment-emergent adverse events with ≥ 5.0% of lenalidomide-treated subjects
  - All treatment-emergent Grade 3 or 4 adverse\events in ≥ 1% of lenalidomide-treated subjects
  - If a term met the algorithm for inclusion in Study MDS-004, the highest frequency of the term was used from either Study MDS-004 or MDS-003.
- Uncontrolled MCL study - MCL-001
  - All treatment-emergent adverse events with ≥ 5.0% of lenalidomide-treated subjects
  - All treatment-emergent Grade 3 or 4 adverse\events in ≥ 2 subjects.

4.8.3 Post-Marketing Experience

The following AEs have been identified during post-marketing use of Revlimid. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Skin and Subcutaneous tissue Disorders[1]: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and DRESS

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps): Tumour Lysis Syndrome, Tumour Flare Reaction

Respiratory, Thoracic and Mediastinal Disorders: Pneumonitis

Cardiac Disorders: Myocardial Infarction

Endocrine disorders: Hyperthyroidism, Hypothyroidism

Hepatobiliary Disorders: Transient abnormal liver laboratory tests, Hepatic failure, Acute hepatic failure, Hepatitis toxic, Cytolytic hepatitis, Cholestatic hepatitis, Mixed cytolytic/cholestatic hepatitis

Infections and infestations: Viral reactivation (such as hepatitis B virus or herpes zoster)

Immune System Disorders[1]**:** Allergic conditions (angioedema, urticaria), Acute graft-versus-host disease (following allogenic hematopoietic transplant), Solid organ transplant rejection

[1] All PTs under MedDRA SMQ of Severe Cutaneous ADRs and HLT rash, and All PTs under HLGT Angioedema and Urticaria will be considered listed

4.8.3.1 Hepatic Disorders

Cases of transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with lenalidomide. For such patients, treatment with lenalidomide should be interrupted and

restarted once the levels return to baseline. Successful re-challenge with lenalidomide, without recurrence of elevated liver laboratory results, was reported in some patients.

4.8.3.2 Thyroid Function

Cases of hypothyroidism and hyperthyroidism have been reported. Optimal control of co-morbid conditions is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

4.8.4 Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no specific experience in the management of lenalidomide overdose in patients with MM, MDS, or MCL. In dose-ranging studies, healthy subjects were exposed to up to 200 mg (administered 100 mg twice daily) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported adverse events. No clinically significant changes in ECGs, blood pressure, or pulse rate were observed.

While no haematologic events were associated with an overdose, such events may be expected since in clinical trials, the dose-limiting toxicity was essentially haematological. In the event of overdose, supportive care is advised. In Australia, contact the Poisons Advisory Centre on 13 11 26 for advice on management. In New Zealand, contact the National Poison Centre on 0800 POISON or 0800 764 766 for advice on management.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Immunomodulating agent

5.1.1 Mechanism of Action

Lenalidomide has a pleiotropic mechanism of action including immunomodulatory, anti-neoplastic, anti-angiogenic, and pro-erythropoietic properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma [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 production of pro-inflammatory cytokines (e.g. TNF-α and IL-6) by monocytes, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, and augments foetal haemoglobin production by CD34+ haematopoietic stem cells.

5.1.2 Cardiac Electrophysiology

A QTc study was conducted to evaluate the effects of lenalidomide on QT interval at single doses of 10 mg and 50 mg. A single dose of lenalidomide up to 50 mg is not associated with prolongation of the QT interval in healthy male subjects. This indicates that lenalidomide is not expected to result in clinically significant prolongation of the QT interval in patients at the approved therapeutic doses.

5.1.3 Clinical Trials

5.1.3.1 Newly Diagnosed Multiple Myeloma (NDMM) in Patients Not Eligible ASCT

Study MM-020 was a Phase III, multicenter, randomised, open-label, 3-arm study to compare the efficacy and safety of lenalidomide and low-dose dexamethasone (Rd) given for 2 different durations of time (i.e., [Arm A: Continuous Rd, until progressive disease] or [Arm B: Rd18, for up to eighteen 28-day cycles {72 weeks}]), to Arm C (melphalan, prednisone and thalidomide [MPT] for a maximum of twelve 42-day cycles [72 weeks]). A total of 1623 subjects with newly diagnosed multiple myeloma (NDMM) (not eligible for autologous stem cell transplantation [ASCT]) were enrolled and randomised in a 1:1:1 ratio to Arm A (n = 535), Arm B (n = 541), or Arm C (n = 547).

Patients in the Continuous Rd arm and the Rd18 arm received lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for the Continuous Rd and Rd18 arms were adjusted according to age and renal function. Patients > 75 years received a dexamethasone dose of 20 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, or low-dose aspirin) during the study.
The primary efficacy endpoint in the study was progression-free survival (PFS). The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, and 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms, with 35% of total patients > 75 years of age.

The study showed a statistically significant prolongation of PFS benefit in patients receiving Continuous Rd (Arm A) compared to MPT (Arm C). The Hazard Ratio was 0.72 ([95% CI: 0.61, 0.85]; p = 0.00006), indicating a 28% decrease in the risk of disease progression for patients treated with Continuous Rd compared with those treated with MPT. The median follow-up time for all surviving subjects at the interim analysis was 37.0 months. The overall response rate (≥ partial response [PR]) was higher in Continuous Rd (75.1%) than in MPT (62.3%) (p < 0.00001). A greater percentage of patients achieved at least a complete response (CR) in Continuous Rd than in MPT (15.1% versus 9.3%, respectively).

The preliminary analysis of the primary comparison of overall survival (OS) shows a reduction of risk of death of 22% in the Continuous Rd Arm compared with the MPT arm. In an updated analysis of OS where the median follow-up time for all surviving subjects was 45.5 months, a further improvement in the reduction of risk of death was noted in the Continuous Rd arm compared with the MPT arm (HR 0.75; p = 0.002). The efficacy results are summarised in Table 7 below.

PFS2 (an exploratory endpoint) was defined for all patients as the time from randomisation to second objective progressive disease (PD), or death from any cause, whichever occurred first. PFS2 was significantly longer in the Continuous Rd arm compared to arm MPT (HR 0.77 [95% CI: 0.65, 0.92]; p = 0.003). The results show a difference in patients who have started 2nd line treatment and type of therapy received: for Continuous Rd, of the 43% who started 2nd line treatment, 62% received bortezomib-containing therapy vs. 12% lenalidomide therapy; for MPT, of the 57% who started 2nd line therapy, 49% received bortezomib-containing therapy vs. 34% lenalidomide therapy.

Table 7. Summary of Efficacy Data from Study MM-020

Endpoint	**Continuous Rd[a] (N = 535)**	**Rd18[b] (N = 541)**	**MPT[c] (N = 547)**
PFS (months)			
Median [95% CI]	25.5 [20.7, 29.4]	20.7 [19.4, 22.0]	21.2 [19.3, 23.2]
HR [95% CI]; p-value			
Rd vs. MPT	0.72 [0.61, 0.85]; p = 0.00006		
Rd vs. Rd18	0.70 [0.60, 0.82]; p = 0.00001		
Rd18 vs. MPT	1.03 [0.89, 1.20]; ns		

Overall Survival (months)*			
Median [95% CI]	58.9 [56.0, NE]	56.7 [50.1, NE]	48.5 [44.2, 52.0]
HR [95% CI]; p-value			
Rd vs. MPT	0.75 [0.62, 0.90]; p = 0.002		
Rd vs. Rd18	0.91 [0.75, 1.09]; ns		
Rd18 vs. MPT	0.83 [0.69, 0.99]; p = 0.034		
Myeloma Response, n (%)			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
ORR (CR, VGPR or PR)	402 (75.1)	397 (73.4)	341 (62.3)
Duration of response (months)			
Median [95% CI]	35.0 [27.9, 43.4]	22.1 [20.3, 24.0]	22.3 [20.2, 24.9]

CI = confidence interval; CR = complete response; HR = hazard ratio; MPT = melphalan, prednisone and thalidomide; NE = not estimable; ns = not significant; ORR = overall response rate; PFS = progression-free survival; PR = partial response; VGPR = very good partial response.
* OS data is based on an updated analysis (03 March 2014).
a = Continuous Rd arm where patients were dosed with lenalidomide + low-dose dexamethasone until progressive disease.
b = Rd18 arm where patients were dosed with lenalidomide + low-dose dexamethasone for up to eighteen 28-day cycles (72 weeks)
c = MPT arm where patients were dosed with melphalan, prednisone and thalidomide for up to twelve 42-day cycles (72 weeks).

5.1.3.2 NDMM in Patients Post-ASCT

The efficacy and safety of lenalidomide maintenance therapy in NDMM patients post-ASCT were assessed in two Phase III, multicenter, randomised, double-blind, 2-arm, parallel group, placebo-controlled studies: Studies CALGB 100104 and IFM 2005-02. The primary endpoint of both studies was PFS (defined from randomisation to the date of progression or death, whichever occurred first). Neither study was powered for the overall survival endpoint.

Study CALGB 100104 recruited patients aged 18-70 years with active NDMM requiring treatment and without prior progression after initial induction therapy. Induction therapy was required to have occurred within 12 months.

Within 90-100 days after high-dose chemotherapy supported by ASCT, patients were randomised 1:1 to receive either lenalidomide or placebo maintenance therapy. The maintenance dose was 10 mg/day continuously (increased up to 15 mg/day after 3 months in the absence of dose-limiting toxicity), and treatment was continued until PD or patient withdrawal for another reason.

In total, 460 patients were randomised: 231 patients to lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

The study was unblinded (upon the recommendation of the data monitoring committee) after surpassing the threshold for a pre-planned interim analysis of PFS. After unblinding, patients in the placebo arm were allowed to cross over to receive lenalidomide before disease progression.

The results of PFS at unblinding (following a pre-planned interim analysis) using a cut off of 17 December 2009 (15.5 months median follow-up), and an updated analysis of PFS and OS using a cut off of 1 February 2016 (81.6 months median follow-up), are presented in Table 8:

Table 8. Summary of Efficacy Data from Study CALGB 100104

Endpoint	Lenalidomide (N = 231)	Placebo (N = 229)
Data at unblinding (17 December 2009)		
Investigator-assessed PFS (months)		
Median [95% CI]	33.9 [NE, NE]	19.0 [16.2, 25.6]
HR [95% CI]; p-value	0.38 [0.27, 0.54]; p < 0.001	
Data at updated analysis (1 February 2016)		
Investigator-assessed PFS (months)		
Median [95% CI]	56.9 [41.9, 71.7]	29.4 [20.7, 35.5]
HR [95% CI]; p-value	0.61 [0.48, 0.76]; p < 0.001	
Overall survival (months)		
Median [95% CI]	111.0 [101.8, NE]	84.2 [80.0, 102.7]
HR [95% CI]; p-value	0.61 [0.46, 0.81]; p < 0.001	

CI = confidence interval; HR = hazard ratio; NE = not estimable; PFS = progression-free survival.

Study IFM 2005-02 recruited patients aged < 65 years at diagnosis who had undergone treatment with high-dose chemotherapy supported by ASCT and had achieved at least a stable disease response at the time of haematologic recovery.

Within 6 months after ASCT, patients were randomised 1:1 to receive either lenalidomide or placebo maintenance therapy. Following 2 courses of lenalidomide consolidation (25 mg/day, Days 1-21 of a 28-day cycle), the maintenance dose was 10 mg/day continuously (increased up to 15 mg/day after 3 months in the absence of dose-limiting toxicity), and treatment was continued until PD or patient withdrawal for another reason.

In total, 614 patients were randomised: 307 patients to lenalidomide and 307 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.
The study was unblinded (upon the recommendation of the data monitoring committee) after surpassing the respective threshold for a pre-planned interim analyses of PFS.

The results of PFS at unblinding (following a pre-planned interim analysis) using a cut off of 7 July 2010 (31.4 months median follow-up), and an updated analysis of PFS and OS using a cut off of 1 February 2016 (96.7 months median follow-up), are presented in Table 9:

Table 9. Summary of Efficacy Data from Study IFM 2005-02

Endpoint	Lenalidomide (N = 307)	Placebo (N = 307)
Data at unblinding (7 July 2010)		
Independent Review Committee-assessed PFS (months)		
Median [95% CI]	41.2 [38.3, -]	23.0 [21.2, 28.0]
HR [95% CI]; p-value	0.50 [0.39, 0.64]; p < 0.001	
Data at updated analysis (1 February 2016)		
Investigator-assessed PFS (months)		
Median [95% CI]	44.4 [39.6, 52.0]	23.8 [21.2, 27.3]
HR [95% CI]; p-value	0.57 [0.47, 0.68]; p < 0.001	
Overall survival (months)		
Median [95% CI]	105.9 [88.8, NE]	88.1 [80.7, 108.4]
HR [95% CI]; p-value	0.90 [0.72, 1.13]; ns	

The efficacy of lenalidomide maintenance versus placebo/no maintenance as a treatment for adult NDMM patients who have undergone ASCT, as measured by overall survival (OS), was further assessed in a meta-analysis of 3 randomised controlled trials (including Studies CALGB 100104, IFM 2005-02

and GIMEMA). A total of 1209 patients are included in the meta-analysis. The demographic and disease characteristics were reflective of a typical transplant-eligible patient population with NDMM.

For the primary analysis using a cut-off of 1 March 2015, the observed HR was 0.74 for lenalidomide versus placebo/no maintenance ([95% CI: 0.62, 0.89]; p = 0.001) indicating a 26% reduction in the risk of death. The median OS was not reached in the lenalidomide maintenance pool and was estimated at 86.0 months ([95% CI: 79.8, 96.0]) in the placebo/no maintenance pool.

An updated OS analysis, using a cut-off of 1 February 2016 (88.8 months median follow-up), continued to show an OS advantage for lenalidomide versus placebo/no maintenance (Table 10).

Table 10. Summary of Efficacy Meta-analysis

Endpoint	Lenalidomide Maintenance Pool (N = 605)	Placebo / No Maintenance Pool (N = 604)
Overall survival (months)		
Median [95% CI]	111.0 [100.7, NE]	86.9 [80.5, 96.0]
HR [95% CI]; p-value	0.77 [0.65, 0.91]; p = 0.002	
Follow-up (months)		
Median	89.6	88.2

CI = confidence interval; HR = hazard ratio; NE = not estimable.

5.1.3.3 Previously Treated Multiple Myeloma (MM)

The efficacy and safety of lenalidomide in MM patients who had received at least one prior treatment 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 high-dose dexamethasone therapy versus high-dose dexamethasone alone. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone (len/dex), 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 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 len/dex group and 176 in the placebo/dex group) and, in total, 351 patients were evaluated in the MM-010 study (176 in the len/dex group and 175 in the placebo/dex group).

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex 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 were the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that len/dex was statistically significantly superior ($p < 0.00001$) to dexamethasone alone for the primary efficacy endpoint, TTP. CR and overall response (OR) rates in the len/dex arm were also significantly higher than the placebo/dex arm in both studies. An extended follow-up efficacy analysis was conducted with a median follow-up of 30.2 months. Table 11 summarises the results of the follow-up efficacy analyses.

Table 11: Summary of Efficacy Analyses - Studies MM-009 and MM-010

Endpoint	MM-009		MM-010	
	Len/Dex N = 177	Placebo/Dex N = 176	Len/Dex N = 176	Placebo/Dex N = 175
TTP (months)				
Median [95% CI]	13.9 [9.5, 17.1]	4.6 [3.7, 5.1]	12.1 [9.4, 19.8]	4.6 [3.8, 4.8]
HR [95% CI]; p-value	0.33 [0.25, 0.44]; p < 0.001		0.36 [0.27, 0.48]; p < 0.001	
Response Rate				
CR, n (%)	28 (16)	4 (2)	30 (17)	7 (4)
PR, n (%)	79 (45)	30 (17)	75 (43)	34 (19)
p-value	< 0.001		< 0.001	
PFS (months)				
Median [95% CI]	12.3 [8.4, 16.7]	4.6 [3.7, 4.7]	10.2 [7.4, 15.2]	4.6 [3.7, 4.7]
HR [95% CI]; p-value	0.36 [0.27, 0.47]; p < 0.001		0.42 [0.32, 0.55]; p <0.001	

CI = confidence interval; CR = complete response; HR = hazard ratio; PFS = progression-free survival; PR = partial response; TTP = time to progression.

5.1.3.4 Myelodysplastic Syndromes (MDS)

The efficacy and safety of Revlimid were evaluated in low- or intermediate-1-risk MDS patients with a deletion-5q (q31-33) cytogenetic abnormality, with or without additional cytogenetic abnormalities, were evaluated in two studies: MDS-003 and MDS-004.

Study MDS-004 was a Phase III, multi-centre, randomised, double-blind, placebo-controlled study in red blood cell (RBC) transfusion-dependent patients. The 52-week double-blind treatment phase included 205 patients who were randomised to receive 10 mg lenalidomide for 21 days of a 28-day cycle, 5 mg lenalidomide continuously, or placebo. The primary efficacy endpoint was transfusion independence at 182 days. The median age of patients was 68.0 years (range 36 to 86), the median duration of MDS was 2.6 years (range 0.2 to 29.2) and 76.1% of patients were females. The study enrolled patients with absolute neutrophil counts (ANC) $\geq 0.5 \times 10^9$/L, platelet counts $\geq 25 \times 10^9$/L, serum creatinine ≤ 2.0 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum total bilirubin ≤ 1.5 mg/dL. An overview of the efficacy results for the Intent-to-Treat (ITT) populations from MDS-004 receiving either cyclic lenalidomide dosing at 10 mg, or placebo, is presented in Table 12.

Study MDS-003 was a Phase II, multi-centre, open-label, single-arm study of 148 patients who were RBC transfusion-dependent. Dosing was primarily at a continuous dose of 10 mg once daily for 28 days, with some experience at a dose of 10 mg daily for 21 of 28 days. The primary efficacy endpoint was RBC transfusion independence of at least 2 months duration, as defined by the MDS International Working Group (IWG) criteria. The median age of patients was 71.0 years (range 37 to 95), the median duration of MDS was 2.5 years (range 0.1 to 20.7) and 65.5% of patients were females. The study enrolled patients with absolute neutrophil counts (ANC) $\geq 0.5 \times 10^9$/L, platelet counts $\geq 50 \times 10^9$/L, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2.0 mg/dL. Table 12 summarises the efficacy results for the ITT population from MDS-003.

In both MDS-003 and MDS-004, granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia.

Table 12: Summary of Efficacy Analyses - Studies MDS-003 and MDS-004

Endpoint	MDS-003	MDS-004*	
	10 mg Continuous	10 mg Cyclic	Placebo
Number RBC-Transfusion Independent at 56 days [a]	97 (65.5%) N=148	42 (60.9%) N=69	5 (7.5%) N=67
Number RBC-Transfusion Independent at 182 days [b]	nr	38 (55.1%) N=69	4 (6.0%) N=67
Median time (range) to transfusion independence (weeks) [c]	4.1 (0.3, 49.0) N=97	4.6 (0.3, 14.7) N=42	0.3 (0.3, 24.1) N=5
Median [95% CI] duration of RBC-transfusion independence (weeks)	114.4 [78.4 – 153.7] N=97	NE [98.3 – NE] N=42	NE [9.1 – NE] N=5
Durability of response – subjects who maintained transfusion independence [d]	40 (41.2%) N=97	30 (71.4%) N=42	4 (80.0%) N=5
Median rise in haemoglobin (g/dL) (range)	5.6 (2.2, 40.7) N=97	6.2 (1.8, 10.0) N=42	2.6 (1.5, 4.4) N=5

Continuous = (28 days of a 28-day cycle); Cyclic = (21 days of a 28-day cycle); CI = confidence interval; RBC = red blood cell; Hb = haemoglobin; NE = not estimable; nr = not reported.

*: Based on RBC-transfusion independence response for subjects who became RBC-transfusion independent for at least 56 days.

a: transfusion independence was defined as the absence of any RBC transfusion during any consecutive 56 days during the treatment period accompanied by at least a 1 g/dL increase in Hb from screening/baseline.

b: RBC-transfusion independence response for subjects who became RBC-transfusion independent for at least 182 days.

c: Measured from the day of the first dose of study drug to the first day of the first 56-day RBC transfusion-free period.

d: Measured from the first of the consecutive 56 days during which the subject was free of RBC transfusions to the date of the first RBC transfusion after this period.

5.1.3.5 Previously Treated Mantle Cell Lymphoma (MCL)

The efficacy and safety of lenalidomide were evaluated in subjects with relapsed/refractory mantle cell lymphoma (MCL) were evaluated in Study MCL-002.

Study MCL-002 was a Phase II, multicenter, randomised, open-label, controlled study to compare the efficacy and safety of single-agent lenalidomide versus single agent of investigator's choice (IC) in subjects with MCL who were refractory to their last regimen or had between 1 and 3 relapses. Patients were randomised 2:1 to the lenalidomide or the control arm. The IC treatment (control arm) was selected before randomisation and consisted of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.
Lenalidomide was administered orally 25 mg once daily for the first 21 days (Day 1 to 21) of repeating 28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.

The primary efficacy endpoint in Study MCL-002 was PFS defined as the time from randomisation to the first observation of disease progression or death due to any cause. OS was a secondary endpoint. Lenalidomide significantly reduced the PFS risk by 39% compared to the control arm (HR 0.61 [95% CI: 0.44, 0.84]; p = 0.004). There was a significant improvement in median PFS for lenalidomide (37.6 weeks [8.7 months]) compared to control (22.7 weeks [5.2 months]).

The key efficacy results from Study MCL-002 are presented in Table 13 below:

Table 13: Summary of Efficacy Analyses for Study MCL-002

Endpoint	Lenalidomide Arm (N = 170)	Control Arm (N = 84)
PFS		
Median [95% CI] (weeks)	37.6 [24.0, 52.6]	22.7 [15.9, 30.1]
Sequential HR [95% CI]; p-value	0.61 [0.44, 0.84]; p = 0.004	
Response, n (%)		
CR	8 (4.7)	0 (0.0)
PR	60 (35.3)	9 (10.7)
SD	50 (29.4)	44 (52.4)
PD	34 (20.0)	26 (31.0)
Not done / missing	18 (10.6)	5 (6.0)
ORR (CR, Cru, PR)		
n (%) [95% CI]	68 (40.0) [32.6, 47.8]	9 (10.7) [5.0, 19.4]
p-value	< 0.001	
CRR (CR, Cru)		
n (%) [95% CI]	8 (4.7) [2.1, 9.1]	0 (0.0) [0.0, 4.3]
p-value	0.043	
DOR		
Median [95% CI] (weeks)	69.6 [41.1, 86.7]	45.1 [36.3, 80.9]
HR [95% CI]	0.70 [0.29, 1.68]	
p-value	0.421	
TTP		
Median [95% CI] (weeks)	39.3 [24.3, 52.9]	24.7 [15.9, 30.1]
HR [95% CI]; p-value	0.62 [0.45, 0.87]; p = 0.005	
OS		
Median [95% CI] (weeks)	121.0 [86.7, 160.4]	91.7 [69.4, 125.6]
HR [95% CI]; p-value	0.89 [0.62, 1.28]; p = 0.519	

CI = confidence interval; CR = complete response; CRR = complete response rate; CRu = complete response unconfirmed; DOR = duration of response; HR = hazard ratio; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TTP = time to progression.

5.2 Pharmacokinetic Properties

5.2.1 Absorption

In healthy volunteers, lenalidomide is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.6 and 1.5 hours post-dose. The maximum concentration (C_{max}) and area-under-the-concentration versus 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. The absolute bioavailability of lenalidomide has not been determined.

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 AUC and 50% decrease in the C_{max} in plasma.

The pharmacokinetics of lenalidomide were very similar in subjects with myelodysplastic syndromes (MDS) compared to subjects with MM. In patients with low- or intermediate-1-risk MDS, a single 10 mg oral dose of lenalidomide was rapidly absorbed with a median time to maximum concentration (t_{max}) of around 1 hour post-dose. The mean terminal half-life ($t_{½}$) was approximately 4 hours. Following multiple dosing of 10 mg per day for 14 days, there was no accumulation of lenalidomide in plasma, with the mean plasma exposure (C_{max} and AUC) and renal clearance at the steady-state comparable to those observed with a single dose. The plasma concentrations 1 hour after dosing were relatively stable for 280 days.

5.2.2 Distribution

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

5.2.3 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 $t_{½}$ of elimination has been observed to increase with dose, from approximately 3 hours at 5 mg up to approximately 9 hours at doses of 400 mg (the higher dose is believed to provide a better estimate of $t_{½}$). Steady-state levels are achieved by Day 4.

Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy volunteers, approximately 90% and 4% of the radioactive dose is eliminated in urine and faeces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide, almost exclusively via the urinary route. 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.

Pharmacokinetic 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 $t_{½}$ 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 4.2.2 [Dose Adjustments].

Pharmacokinetic analyses based on MM 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 MM patients. Exposure in MM 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 MM 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 MM 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

5.3.1 Genotoxicity

In vitro (mutation in bacteria, chromosomal aberration in human lymphocytes, mutation in mouse lymphoma cells, and Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) genotoxicity studies revealed no drug-related effects at either the gene or chromosomal level.

5.3.2 Carcinogenicity

Carcinogenicity studies with lenalidomide have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Revlimid capsules contain the following excipients: lactose; cellulose, microcrystalline; croscarmellose sodium; and magnesium stearate.

The capsule shells contain gelatine, titanium dioxide (E171), black ink, and the following colourants: 2.5 mg (FD&C Blue#2 [indigo carmine; E132], and yellow iron oxide [E172]); 7.5 mg (yellow iron oxide [E172]); 10 mg (FD&C Blue#2 [E132], and yellow iron oxide [E172]); 15 mg (FD&C Blue#2 [E132]; and 20 mg (FD&C Blue#2 [E132], and yellow iron oxide [E172]).

The black printing ink used on the capsules contains shellac, ethanol, isopropyl alcohol, butan-1-ol, propylene glycol, water-purified, strong ammonia solution, potassium hydroxide, and black iron oxide [E172].

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

3 Years.

6.4 Special Precautions for Storage

Store below 25°C. Store in the original package.

6.5 Nature and Contents of Container

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

Revlimid is available as 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules in blister packs containing 21 capsules each. However, not all strengths are being distributed in Australia.

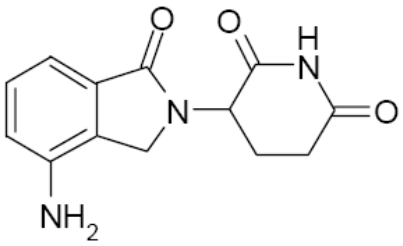
6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physiochemical Properties

Molecular formula:	$C_{13}H_{13}N_3O_3$
Molecular weight:	259.25 g/mol
ATC code:	L04 AX04
Chemical name:	3-(4'-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione
Chemical Abstract Service (CAS) registry number:	191732-72-6

Chemical structure:



7 MEDICINE SCHEDULE (POISONS SCHEDULE)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Sponsored in Australia by:

Celgene Pty Limited
Level 15, 60 City Road
Southbank VIC 3006
Australia.
Telephone: 1800 CELGENE (1800 235 4363)

9 DATE OF FIRST APPROVAL

20 December 2007

10 DATE OF REVISION

25 January 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Whole PI	Reformatted to align with the proposed new format by the TGA.
4.1	New indication added. *Revlimid is indicated for the maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.*
4.2	Dosage and Dose Adjustment sections updated with details relating to the new indication.
4.8	Adverse Events and Adverse Reactions sections updated with details relating to the new indication.
4.8	Post Marketing Experience section reformatted and updated to add solid organ transplant rejection as an ADR
5.1.3	Clinical trial details relating to the New indication added.