FULL PRESCRIBING INFORMATION

WARNING: EMBRYO FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. In women of childbearing potential, obtain a negative pregnancy test before starting REVLIMID treatment. Women of childbearing potential must use 2 reliable forms of contraception simultaneously or continuously abstain from heterosexual sex 4 weeks before starting treatment, during (including dose interruptions) and for 4 weeks following discontinuation of REVLIMID treatment [*see Warnings and Precautions (5.1)*]. To avoid fetal exposure to lenalidomide, REVLIMID is only available under a restricted distribution program called "Revlimid RMP-PPP (5.2).

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts 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 use of blood product support and/or growth factors *[see Dosage and Administration (2.2)]*.

Venous and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction, and stroke in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylasis is recommended and the choice of regimen should be based on an assessment of an individual patient's underlying risk factors [*see Warnings and Precautions (5.4)*].

1. INDICATIONS AND USAGE

1.1 Multiple Myeloma

REVLIMID is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

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

1.2 Myelodysplastic Syndromes

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

1.3 Mantle Cell Lymphoma

REVLIMID as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL.

REVLIMID 7.5mg is indicated for Multiple Myeloma only.

1.4 Limitations of Use

REVLIMID is not indicated and is not recommended for the treatment of patients with CLL outside of controlled clinical trials [*see Warnings and Precautions (5.5)*].

2. DOSAGE AND ADMINISTRATION

REVLIMID should be taken orally at about the same time each day, either with or without food. REVLIMID hard capsules should be swallowed whole with water. The hard capsules should not be opened, broken, or chewed.

2.1 Newly Diagnosed Multiple Myeloma

Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance.
Dosing is continued or modified based upon clinical and laboratory findings. For patients ≥75 years of age, the starting dose of dexamethasone is 20 mg/day on days 1, 8, 15 and 22 of each 28-day treatment cycle. The recommended dose of lenalidomide for patients suffering from moderate renal impairment is 10 mg once daily.

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

- *Dose reduction steps*

	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	NA

- *Thrombocytopenia*

When platelets	Recommended course
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 resumed at next cycle

[a] If Dose Limiting Toxicity (DLT) occurs on > day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

In case of neutropenia, the use of growth factors in patient management should be considered. If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with lenalidomide alone, 10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression. Dosing is continued or modified based upon clinical and laboratory findings.

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

- *Dose reduction steps*

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg

Dose level -1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose level -2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose level -3	2.5 mg	NA	0.25 mg/kg

[a] *If neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide*

- *Thrombocytopenia*

When platelets	Recommended course
First fall to < 25 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/L	Resume lenalidomide and melphalan at Dose level -1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily.

- *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L[a]	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

[a] *If the subject has not been receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue G-CSF as needed and maintain dose of melphalan if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.*

In case of neutropenia, the use of growth factors in patient management should be considered.

For patients older than 75 years of age treated with lenalidomide in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on days 1, 8, 15 and 22 of each 28-day treatment cycle.

No dose adjustment is proposed for patients older than 75 years treated with lenalidomide in combination with melphalan and prednisone.

2.2 Multiple Myeloma with at least one prior therapy

The recommended starting dose of REVLIMID is 25 mg once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg 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 orally on days 1-4 every 28 days. Treatment is continued or modified based upon clinical and laboratory findings.
Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Lenalidomide treatment must not be started if the ANC < 1,000/mcL, and/or platelet counts < 75,000/ mcL or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30,000/mcL.

Dose Adjustments for Hematologic Toxicities During Multiple Myeloma Treatment
Dose modification guidelines, as summarized below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to REVLIMID.

Platelet counts

Thrombocytopenia in MM

When Platelets	Recommended Course
Fall to <30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥30,000/mcL	Restart REVLIMID at 15 mg daily
For each subsequent drop <30,000/mcL	Interrupt REVLIMID treatment
Return to ≥30,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

Absolute Neutrophil counts (ANC)
Neutropenia in MM

When Neutrophils	Recommended Course
Fall to <1000/mcL	Interrupt REVLIMID treatment, add G-CSF, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume REVLIMID at 25 mg daily
Return to ≥1,000/mcL and if other toxicity	Resume REVLIMID at 15 mg daily
For each subsequent drop <1,000/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg less than the previous dose. Do not dose below 5 mg daily

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

Starting Dose Adjustment for Renal Impairment in MM:

See Section 2.5

2.3 Myelodysplastic Syndromes

The recommended starting dose of REVLIMID is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MDS Treatment
Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet counts
If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥100,000/mcL	
When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt REVLIMID treatment
Return to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt REVLIMID treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:
If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt REVLIMID treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID at 2.5 mg daily

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:
Absolute Neutrophil counts (ANC)
If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ANC ≥1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <750/mcL	Interrupt REVLIMID treatment
Return to ≥1,000/mcL	Resume REVLIMID at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <500/mcL	Interrupt REVLIMID treatment

Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	Recommended Course
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:
If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	Recommended Course
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID treatment
Return to ≥500/mcL	Resume REVLIMID at 2.5 mg daily

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

Starting Dose Adjustment for Renal Impairment in MDS:

See Section 2.5

2.4 Mantle Cell Lymphoma

The recommended starting dose of REVLIMID is 25 mg/day orally on days 1-21 of repeated 28-day cycles.
Dosing is continued or modified based upon clinical and laboratory findings.

Dose reduction steps

Starting dose	25 mg once daily on days 1-21, every 28 days
Dose Level -1	20 mg once daily on days 1-21, every 28 days
Dose Level -2	15 mg once daily on days 1-21, every 28 days
Dose Level -3	10 mg once daily on days 1-21, every 28 days
Dose Level -4	5 mg once daily on days 1-21, every 28 days
Dose Level -5	2.5 mg once daily on days 1-21, every 28 days 5 mg every other day on days 1-21, every 28 days

Thrombocytopenia

When Platelets	Recommended Course
Fall to <50 x 10^9/L	Interrupt REVLIMID treatment and conduct Complete Blood Count (CBC) at least every 7 days

Return to ≥ 60 x 10^9/L	Resume lenalidomide at next lower level (Dose Level -1)
For each subsequent drop below 50 x 10^9/L	Interrupt REVLIMID treatment and conduct the CBC at least every 7 days
Return to ≥60 x 10^9/L	Resume REVLIMID at next lower level (Dose Level -2, -3, -4 or -5). Do not dose below Dose Level -5

Neutropenia

When Neutrophils	**Recommended Course**
Fall to <1 x 10^9/L for at least 7 days OR Falls to <1 x 10^9/L with an associated fever (body temperature ≥ 38.5°C) OR Falls to <0.5 x 10^9/L	Interrupt REVLIMID treatment and conduct the CBC at least every 7 days
Return to ≥1 x 10^9/L	Resume REVLIMID at next lower dose level (Dose Level – 1)
For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt REVLIMID treatment
Returns to ≥1 x 10^9/L	Resume REVLIMID at next lower dose level (Dose Level -2, -3, -4, -5). Do not dose below Dose Level -5

Tumour flare reaction

REVLIMID may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with REVLIMID 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.

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

Starting Dose Adjustment for Renal Impairment in MCL:

See Section 2.5.

2.5 Starting Dose for Renal Impairment in MM, MDS or MCL

Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic

study in patients with renal impairment due to non-malignant conditions, REVLIMID starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with MM, MDS or MCL are as follows:

Starting Dose Adjustments for Patients with Renal Impairment in MM, MDS or MCL

Category	Renal Function (Cockcroft-Gault)	Dose in MM or MCL	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	10 mg Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	7.5 mg Every 24 hours	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose following dialysis.	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of REVLIMID therapy, subsequent REVLIMID dose modification is based on individual patient treatment tolerance, as described elsewhere (see section 2).

All patients
For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

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

3. DOSAGE FORMS AND STRENGTHS

REVLIMID 2.5 mg, 5 mg, 7.5mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules will be supplied through the Revlimid RMP-PPP.

REVLIMID is available in the following hard capsule strengths:

2.5 mg: White and blue-green opaque hard capsules imprinted "REV" on one half and "2.5 mg" on the other half in black ink
5 mg: White opaque hard capsules imprinted "REV" on one half and "5 mg" on the other half in black ink
7.5mg: Pale yellow/white hard capsules marked "REV 7.5 mg"
10 mg: Blue/green and pale yellow opaque hard capsules imprinted "REV" on one half and "10 mg" on the other half in black ink
15 mg: Powder blue and white opaque hard capsules imprinted "REV" on one half and "15 mg" on the other half in black ink

20 mg: Powder blue and blue-green opaque hard capsules imprinted “REV” on one half and “20 mg” on the other half in black ink
25 mg: White opaque hard capsules imprinted “REV” on one half and “25 mg” on the other half in black ink

4. CONTRAINDICATIONS

4.1 Pregnancy

REVLIMID can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide’s structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant [*see Boxed Warning*].Females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy.
If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.
Females of childbearing potential being treated with REVLIMID must have pregnancy testing (sensitivity of at least 25 mIU/mL). The test should be performed prior to beginning therapy within 3 days prior to prescribing REVLIMID and then monthly thereafter (including dose interruptions). **Pregnancy testing should be performed also 4 weeks following discontinuation of REVLIMID therapy.**
Pregnancy testing and counseling must be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, REVLIMID must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.
If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Warnings and Precautions (5.1, 5.2), Use in Special Populations (8.1), (8.5)*].

REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide [*see Warnings and Precautions (5.8)*].

5. WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

REVLIMID is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death [*see Use in Specific Populations (8.1)*]. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.
If REVLIMID is used during pregnancy, it may cause birth defects or death to a developing baby. Females of childbearing potential must be advised to avoid pregnancy while on REVLIMID. Two reliable forms of contraception should be used simultaneously during therapy, during dose interruptions and for at least 4 weeks following discontinuation of therapy.
There are no adequate and well-controlled studies in pregnant females.

REVLIMID is only available through the RMP-PPP

5.2 Reproductive Risk and Special Prescribing Requirements (Revlimid RMP-PPP)

Because of this potential toxicity and to avoid fetal exposure, REVLIMID is only available under a special restricted distribution program called "Revlimid RMP-PPP". Prescribers and pharmacists registered with the program can prescribe and dispense the product to patients who are registered and meet all the conditions of the Revlimid RMP-PPP.
Please see the following information for prescribers, female patients, and male patients about this restricted distribution program.

Revlimid RMP-PPP
Prescribers
REVLIMID can be prescribed only by licensed prescribers who are registered in the Revlimid RMP-PPP and understand the potential risk of teratogenicity if lenalidomide is used during pregnancy.

Female Patients:
Two effective contraception methods must be used by female patients of childbearing potential for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for 4 weeks following discontinuation of REVLIMID therapy unless continuous abstinence from heterosexual sexual contact is the chosen method. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy, a bilateral oophorectomy, because the patient has been postmenopausal naturally for at least 24 consecutive months or in any other case indicated in Revlimid RMP-PPP. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy, who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) or in any other case indicated in the Revlimid RMP-PPP, are considered to be females of childbearing potential.

Cecession of menses due to anti-cancer therapy, do not exclude the potential to become pregnant.

Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method.
Females of childbearing potential must have a negative pregnancy test (sensitivity of at least 25 mIU/mL) before starting the therapy, and then monthly thereafter (including dose interruptions and including 4 weeks following discontinuation of REVLIMID therapy). The test should be performed within 3 days prior to prescribing REVLIMID. A prescription for REVLIMID for a female of childbearing potential must not be issued by the prescriber until a negative pregnancy test has been verified by the prescriber.
Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. REVLIMID therapy must be discontinued during this evaluation.
Pregnancy test results should be verified by the prescriber prior to dispensing **any** prescription.
If pregnancy does occur during treatment, REVLIMID must be discontinued immediately.

Any suspected fetal exposure to REVLIMID must be reported to the attending physician and Neopharm. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.
Do not breastfeed during therapy (including dose interruptions) and for 4 weeks after discontinuation of therapy.

Patients should not donate blood while taking REVLIMID, during any breaks (discontinuations) in your therapy, and for 4 weeks following discontinuation of REVLIMID therapy.

Male Patients:
Clinical data has demonstrated the presence of lenalidomide in human semen. Therefore, males receiving REVLIMID must always use a latex/ polyurethane condom during any sexual contact with females of childbearing potential, even if they have undergone a successful vasectomy. In the case of a male patient with an allergy to latex or polyurethane, at least one highly effective form of contraception should be used by any female sexual partner. Contraception should be started in this partner at least 4 weeks prior to the start of a sexual relationship with the patient, and continued throughout REVLIMID therapy including dose interruptions and for 4 weeks following discontinuation of therapy.
Patients should not donate blood and semen or sperm while taking REVLIMID, during any breaks (discontinuations) in your therapy, and for 4 weeks following discontinuation of REVLIMID therapy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should be performed every 4 weeks.

Pregnancy testing should be performed also 4 weeks following discontinuation of REVLIMID therapy.

Female Patients
REVLIMID may be used in females of childbearing potential only when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is unable to become pregnant while on REVLIMID therapy):

- she is capable of complying with the mandatory contraceptive measures/ abstinence from heterosexual sexual contact, pregnancy testing, and patient registration as described in the Revlimid RMP-PPP.
- she has received and understands both oral and written warnings of the potential risks of taking REVLIMID during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, patch or implants) or male partner's vasectomy and one additional effective contraceptive method – latex/ polyurethane condom by her male partner, diaphragm or cervical cap), unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature females who have not undergone a hysterectomy, who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months), who have not had a bilateral oophorectomy or in any other case indicated in the Revlimid RMP-PPP, are considered to be females of childbearing potential.
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception simultaneously for 4 weeks prior to beginning

REVLIMID therapy, during therapy, during dose interruptions and for 4 weeks after discontinuation of therapy.

- she has had a negative pregnancy test with a sensitivity of at least 25 mIU/mL, within 3 days prior to beginning therapy (3 days prior to prescribing REVLIMID).
- if the patient is a child or adolescent of child bearing potential her parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

Male Patients

REVLIMID may be used in sexually active males when the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, and patient registration as described in the Revlimid RMP-PPP.
- he has received and understands both oral and written warnings of the potential risks of taking REVLIMID and exposing a fetus to the drug.
- he has received both oral and written warnings of the risk of possible contraception failure and that it is known that lenalidomide is present in semen. He has been instructed that he must always use a latex/ polyurethane condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy. Females of childbearing potential are considered to be sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy, who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) or in any other case indicated in the Revlimid RMP-PPP. In the case of a male patient with an allergy to latex or polyurethane, at least one highly effective form of contraception should be used by any female sexual partner. Contraception should be started in this partner at least 4 weeks prior to the start of a sexual relationship with the patient, and continued throughout REVLIMID therapy including dose interruptions and for 4 weeks following discontinuation of therapy.
- he acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy.
- if the patient is a child or adolescent his parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction [*see Dosage and Administration (2.1,* 2.2, 2.3*)*].

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 6.2). Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. 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 [*see Boxed Warning and Dosage and Administration (2.2)*].

- Multiple myeloma with at least one prior therapy

In the pooled MM trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone [*see Adverse Reactions (6.1)*].

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with low dose dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm. Patients should be advised to promptly report febrile episodes and dose reductions may be required.

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding.

- Newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with melphalan and prednisone

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide (MPR+R) and melphalan, prednisone and lenaldiomide followed by placebo (MPR+p) treated patients compared with 7.8% in MPp+p-treated patients;). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients;).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products that increase susceptibility to bleeding.

- Mantle cell lymphoma

Lenalidomide treatment in mantle cell lymphoma patients is associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm.
Tumour flare reaction and tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with

lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The 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 have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.

Tumour burden

- Mantle cell lymphoma

Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available.

Early death

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, there were 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (40%) and 6/28 (21%) (See section 5.1).

Adverse events

In study MCL-002, during treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).
Patients with high tumour burden should therefore be closely monitored for adverse reactions (see Section 4.8) including signs of tumour flare reaction (TFR). Please refer to section 4.2 for dose adjustments for TFR.
High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tumour flare reaction

- Mantle cell lymphoma

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 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 (see section 4.2).

Infection with or without Neutropenia

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was observed with lenalidomide in combination with dexamethasone than with MPT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (e.g., cough, fever, etc.) thereby allowing for early management to reduce severity.

Cases of viral reactivation have been reported in patients receiving lenalidomide, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

Some of the cases of viral reactivation had a fatal outcome.

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster requiring a temporary hold or permanent discontinuation of the treatment with lenalidomide and adequate antiviral treatment.

Reactivation of hepatitis B has been reported rarely in patients receiving lenalidomide who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure resulting in discontinuation of lenalidomide and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when lenalidomide is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

5.4 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thrombosis are increased in patients treated with REVLIMID. A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in a clinical trials with varying use of anticoagulant therapies. [*see Boxed Warning and Adverse Reactions (6.1)*].
Venous thromboembolism was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone in newly diagnosed multiple myeloma and with monotherapy in myelodysplastic syndromes.

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with multiple myeloma who were treated with REVLIMID and dexamethasone therapy compared to patients treated within the placebo plus dexamethasone group (0.6%, and 0.9%) in clinical trials [*see Adverse Reactions (6.1)*]. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).
In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed multiple myeloma who were treated with REVLIMID and dexamethasone compared to 8.3% thrombosis in patients treated with in placebo and dexamethasone. The median time to first thrombosis event was 2.7 months. thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risk. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving REVLIMID [*see Drug Interactions (7.3*)].

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on

the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08 – 3.41], consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.
Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

5.6 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide
In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In clinical trials of newly diagnosed multiple myeloma patients eligible for transplant, an increased incidence rate of hematologic SPM has been observed in patients receiving lenalidomide immediately following high-dose melphalan and Autologous Stem Cell Transplant (ASCT) compared with patients who received placebo (1.27 to 1.56 versus 0.46 to 0.53 per 100 person-years, respectively). Cases of B-cell malignancies (including Hodgkin's lymphoma) observed in the clinical trials were in patients who received lenalidomide in the post-ASCT setting.

Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.7 Hepatotoxicity
Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed

characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics and older age might be risk factors. Monitor liver enzymes periodically. Stop Revlimid upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

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

5.8 Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. 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 SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

REVLIMID hard capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance.

5.11 Newly diagnosed multiple myeloma patients

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min.

5.12 Cataract

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone particularly when used for a prolonged time. Regular monitoring of visual ability is recommended.

5.13 Peripheral neuropathy

There was no increase in peripheral neuropathy observed with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other sections of the prescribing information:

- Embryo-Fetal Toxicity [*see Boxed Warnings, Warnings and Precautions (5.1, 5.2)*]

- Neutropenia and thrombocytopenia [*see Boxed Warnings, Warnings and Precautions (5.3)*]
- Venous and arterial thromboembolism [*see Warnings and Precautions (5.4)]*
- Increased Mortality in Patients with CLL [*see Warnings and Precautions (5.5)]*
- Second Primary Malignancies [*see Warnings and Precautions (5.6)*]
- Hepatotoxicity [*see* Warnings *and Precautions (5.7)*]
- Allergic Reactions [*see Warnings and Precautions (5.8)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.9)*]
- Tumor flare reactions [*see Warnings and Precautions (5.10)*]
- Cataract [*see Warnings and Precautions (5.11)*]
- Peripheral Neuropathy [*see Warnings and Precautions (5.12)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Multiple Myeloma

Summary of the safety profile in newly diagnosed multiple myeloma in patients treated with lenalidomide in combination with low dose dexamethasone:

The serious adverse reactions observed more frequently (≥5%) with lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Summary of the safety profile in newly diagnosed multiple myeloma patients treated with lenalidomide in combination with melphalan and prednisone:

The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

The adverse reactions observed more frequently with MPR+R or MPR+ p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).*Summary of the safety profile in multiple myeloma patients with at least one prior therapy*

In two Phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:

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

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Mantle cell lymphoma

The overall safety profile of Revlimid in patients with mantle cell lymphoma is based on data from 254 patients from a Phase II randomized, controlled study MCL-002.
Additionally, ADRs from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in Study MCL-002 (with a difference of at least 2 percentage points) in the lenalidomide arm compared with the control arm were:

- Neutropenia (3.6%)
- Pulmonary embolism (3.6%)
- Diarrhoea (3.6%)

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in Study MCL-002 were neutropenia (50.9%), anaemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%).
During treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%). High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Tabulated summary of adverse reactions for combination therapy

The adverse reactions observed in patients treated for multiple myeloma are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal multiple myeloma studies.

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

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

System Organ Class / Preferred Term	**All ADRs/Frequency**	**Grade 3−4 ADRs/Frequency**
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis Common Sepsis, Sinusitis	Common Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma Squamous skin cancer^*	Common Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin** Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia, Thrombocytopenia, Anaemia, Haemorrhagic disorder, Leucopenias Common Febrile neutropenia, Pancytopenia Uncommon Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	Very Common Neutropenia, Thrombocytopenia, Anaemia, Leucopenias Common Febrile neutropenia, Pancytopenia, Haemolytic anaemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration	Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired	Common Cerebrovascular accident, Dizziness, Syncope Uncommon Intracranial haemorrhage, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute) , Atrial fibrillation, Congestive cardiac failure, Tachycardia, Cardiac failure, Myocardial ischaemia
Vascular Disorders	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism Common Hypotension, Hypertension, Ecchymosis	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea, Epistaxis	Common Respiratory distress, Dyspnoea

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding), Dry mouth, Stomatitis, Dysphagia Uncommon Colitis, Caecitis	Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting
Hepatobiliary Disorders	Common Abnormal liver function tests Uncommon Hepatic failure	Common Cholestasis, Abnormal liver function tests Uncommon Hepatic failure
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia Common Muscular weakness, Joint swelling, Myalgia	Common Muscular weakness, Bone pain Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute) Common Haematuria, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy	Common Fatigue, Pyrexia, Asthenia

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Investigations	Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls

** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Venous and Arterial Thromboembolism [*see Warnings and Precautions (5.4)*]

Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively. in the 2 studies in patients with at least 1 prior therapy with discontinuations due to DVT adverse reactions reported at comparable rates between groups. In the NDMM study, DVT was reported as an adverse reaction (all grades: 10.3%, 7.2%, 4.1%), as a serious adverse reaction (3.6%, 2.0%, 1.7%), and as a Grade 3/4 adverse reaction (5.6%, 3.7%, 2.8%) in the Rd Continuous, Rd18, and MPT Arms, respectively. Discontinuations and dose reductions due to DVT adverse reactions were reported at comparable rates between the Rd Continuous and Rd18 Arms (both <1%). Interruption of REVLIMID treatment due to DVT adverse reactions was reported at comparable rates between the Rd Continuous (2.3%) and Rd18 (1.5%) arms.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (0%) at a higher rate in the REVLIMID/dexamethasone group compared to 0.9% (serious or grade ¾) in the placebo/dexamethasone group in the 2 studies in patients with at least 1 prior therapy, with discontinuations due to PE adverse reactions were at comparable rates between groups. In the NDMM study (MM-020), the frequency of adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms for adverse reactions (all grades: 3.9%, 3.3%, and 4.3%, respectively), serious adverse reactions (3.8%, 2.8%, and 3.7%, respectively), and grade 3/4 adverse reactions (3.8%, 3.0%, and 3.7%, respectively).

Myocardial infarction was reported as a serious (1.7%) or severe (1.7%) adverse drug reaction at a higher rate in the REVLIMID/dexamethasone group compared to 0.6 % and 0.6% respectively in the placebo/dexamethasone group. Discontinuation due to MI (including acute) adverse reactions was low, 0.8% in REVLIMID/dexamethasone group and none in the placebo/dexamethasone group. In the NDMM study, myocardial infarction (including acute) was reported as an adverse reaction (all grades: 2.4%, 0.6%, and 1.1%), as a serious adverse reaction, (2.3%, 0.6%, and 1.1%), or as a severe adverse reaction (1.9%, 0.6%, and 0.9%) in the Rd Continuous, Rd18, and MPT Arms, respectively.

Stroke (CVA) was reported as a serious (2.3%) or severe (2.0%) adverse drug reaction in the REVLIMID/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in REVLIMID/ dexamethasone group and 0.3% in the placebo/dexamethasone group. In the NDMM study, CVA was reported as an adverse reaction (all grades: 0.8%, 0.6%, and 0.6%), as a serious adverse reaction (0.8%, 0.6 %, and 0.6%), or as a severe adverse reaction (0.6%, 0.6%, 0.2%) in the Rd Continuous, Rd18, and MPT arms respectively.

Other Adverse Reactions After At Least One Prior Therapy for Multiple Myeloma
In these studies, the following adverse drug reactions (ADRs) not described above that occurred at ≥1% rate and of at least twice of the placebo percentage rate were reported:
Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia
Cardiac disorders: bradycardia, myocardial infarction, angina pectoris
Endocrine disorders: hirsutism
Eye disorders: blindness, ocular hypertension, reduced visual acuity
Ear and Labyrinth Disorders: deafness
Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia
General disorders and administration site conditions: influenza-like illness (includes pyrexia, myalgia, musculoskeletal pain, headache and rigors), malaise
Investigations: liver function tests abnormal, alanine aminotransferase increased
Neoplasms benign, malignant and unspecified: basal cell carcinoma
Nervous system disorders: cerebral ischemia
Psychiatric disorders: mood swings, hallucination, loss of libido
Reproductive system and breast disorders: erectile dysfunction
Respiratory, thoracic and mediastinal disorders: cough, hoarseness
Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation
In other clinical studies of REVLIMID in MM patients, the following serious or nonserious adverse events (regardless of relationship to study drug treatment) not described in Tables attached were reported:
Ear and Labyrinth Disorders: tinnitus, hypoacusis
Gastrointestinal disorders: colitis, caecitis
Renal & urinary disorders: Fanconi syndrome, renal tubular necrosis
Skin and subcutaneous tissue disorders: photosensitivity reaction

6.2 Clinical Trials Experience in Myelodysplastic Syndromes

A total of 148 patients received at least 1 dose of 10 mg REVLIMID in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of REVLIMID. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 2 summarizes the adverse events that were reported in ≥ 5% of the REVLIMID treated patients in the del 5q MDS clinical study. Table 3 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with REVLIMID. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 2: Summary of Adverse Events Reported in ≥5% of the REVLIMID Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	10 mg Overall (N=148)	
Patients with at least one adverse event	148	(100.0)
Blood and Lymphatic System Disorders		
Thrombocytopenia	91	(61.5)
Neutropenia	87	(58.8)

Anemia	17	(11.5)
Leukopenia	12	(8.1)
Febrile Neutropenia	8	(5.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	62	(41.9)
Rash	53	(35.8)
Dry Skin	21	(14.2)
Contusion	12	(8.1)
Night Sweats	12	(8.1)
Sweating Increased	10	(6.8)
Ecchymosis	8	(5.4)
Erythema	8	(5.4)
Gastrointestinal Disorders		
Diarrhea	72	(48.6)
Constipation	35	(23.6)
Nausea	35	(23.6)
Abdominal Pain	18	(12.2)
Vomiting	15	(10.1)
Abdominal Pain Upper	12	(8.1)
Dry Mouth	10	(6.8)
Loose Stools	9	(6.1)
Respiratory, Thoracic and Mediastinal Disorders		
Nasopharyngitis	34	(23.0)
Cough	29	(19.6)
Dyspnea	25	(16.9)
Pharyngitis	23	(15.5)
Epistaxis	22	(14.9)
Dyspnea Exertional	10	(6.8)
Rhinitis	10	(6.8)
Bronchitis	9	(6.1)
General Disorders and Administration Site Conditions		
Fatigue	46	(31.1)
Pyrexia	31	(20.9)
Edema Peripheral	30	(20.3)
Asthenia	22	(14.9)
Edema	15	(10.1)
Pain	10	(6.8)
Rigors	9	(6.1)
Chest Pain	8	(5.4)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	32	(21.6)
Back Pain	31	(20.9)
Muscle Cramp	27	(18.2)
Pain in Limb	16	(10.8)
Myalgia	13	(8.8)
Peripheral Swelling	12	(8.1)
Nervous System Disorders		
Dizziness	29	(19.6)
Headache	29	(19.6)
Hypoesthesia	10	(6.8)
Dysgeusia	9	(6.1)

Peripheral Neuropathy	8	(5.4)
Infections and Infestations		
Upper Respiratory Tract Infection	22	(14.9)
Pneumonia	17	(11.5)
Urinary Tract Infection	16	(10.8)
Sinusitis	12	(8.1)
Cellulitis	8	(5.4)
Metabolism and Nutrition Disorders		
Hypokalemia	16	(10.8)
Anorexia	15	(10.1)
Hypomagnesemia	9	(6.1)
Investigations		
Alanine Aminotransferase Increased	12	(8.1)
Psychiatric Disorders		
Insomnia	15	(10.1)
Depression	8	(5.4)
Renal and Urinary Disorders		
Dysuria	10	(6.8)
Vascular Disorders		
Hypertension	9	(6.1)
Endocrine Disorders		
Acquired Hypothyroidism	10	(6.8)
Cardiac Disorders		
Palpitations	8	(5.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes
and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple
occurrences of an AE is counted only once in the AE category.

Table 3: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	**10 mg (N=148)**	
Patients with at least one Grade 3/4 AE	131	(88.5)
Neutropenia	79	(53.4)
Thrombocytopenia	74	(50.0)
Pneumonia	11	(7.4)
Rash	10	(6.8)
Anemia	9	(6.1)
Leukopenia	8	(5.4)
Fatigue	7	(4.7)
Dyspnea	7	(4.7)
Back Pain	7	(4.7)
Febrile Neutropenia	6	(4.1)
Nausea	6	(4.1)

Diarrhea	5	(3.4)
Pyrexia	5	(3.4)
Sepsis	4	(2.7)
Dizziness	4	(2.7)
Granulocytopenia	3	(2.0)
Chest Pain	3	(2.0)
Pulmonary Embolism	3	(2.0)
Respiratory Distress	3	(2.0)
Pruritus	3	(2.0)
Pancytopenia	3	(2.0)
Muscle Cramp	3	(2.0)
Respiratory Tract Infection	2	(1.4)
Upper Respiratory Tract Infection	2	(1.4)
Asthenia	2	(1.4)
Multi-organ Failure	2	(1.4)
Epistaxis	2	(1.4)
Hypoxia	2	(1.4)
Pleural Effusion	2	(1.4)
Pneumonitis	2	(1.4)
Pulmonary Hypertension	2	(1.4)
Vomiting	2	(1.4)
Sweating Increased	2	(1.4)
Arthralgia	2	(1.4)
Pain in Limb	2	(1.4)
Headache	2	(1.4)
Syncope	2	(1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.

[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

In other clinical studies of REVLIMID in MDS patients, the following serious adverse events (regardless of relationship to study drug treatment) not described in Table 5 or 6 were reported:

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia
Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction
Ear and labyrinth disorders: vertigo
Endocrine disorders: Basedow's disease
Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage
General disorders and administration site conditions: disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure
Immune system disorders: hypersensitivity
Infections and infestations infection bacteremia, central line infection, clostridial infection, ear infection, *Enterobacter* sepsis, fungal infection, herpes viral infection NOS, influenza, kidney infection, *Klebsiella* sepsis, lobar pneumonia, localized infection, oral infection, *Pseudomonas* infection, septic shock, sinusitis acute, sinusitis, *Staphylococcal* infection, urosepsis
Injury, poisoning and procedural complications: femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis, hip fracture, overdose, post procedural hemorrhage, rib fracture, road traffic accident, spinal compression fracture
Investigations: blood creatinine increased, hemoglobin decreased, liver function tests abnormal, troponin I increased
Metabolism and nutrition disorders: dehydration, gout, hypernatremia, hypoglycemia
Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate
Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid leukemia, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma, prostate cancer metastatic
Nervous system disorders: cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine, spinal cord compression, subarachnoid hemorrhage, transient ischemic attack
Psychiatric disorders: confusional state
Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass
Reproductive system and breast disorders: pelvic pain
Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing
Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis
Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, ischemia, thrombophlebitis superficial, thrombosis

6.3 Clinical Trials Experience in Mantle Cell Lymphoma

In the MCL trial, a total of 134 patients received at least 1 dose of REVLIMID. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 4 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with REVLIMID. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

Table 4: ADRs reported in clinical trials in patients with mantle cell lymphoma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pneumonia Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections) ◊, Pneumonia◊
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer^◊, Basal cell Carcinoma◊
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia, Neutropenia, Leucopenias, Anaemia Common Febrile neutropenia	Very Common Thrombocytopenia, Neutropenia◊, Anaemia◊ Common Febrile neutropenia^◊, Leucopenias◊
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydratation,	Common Dehydration◊, Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System Disorders	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Acute myocardial infarction (including acute) ◊, Cardiac failure
Vascular Disorders	Common Hypotension	Common Deep vein thrombosis◊, pulmonary embolism^◊, Hypotension◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoeia	Common Dyspnoeia◊

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Gastrointestinal Disorders	Very Common Diarrhoea, Nausea◊, Vomiting◊, Constipation Common Abdominal pain	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough) Common Chills	Common Pyrexia◊, Asthenia◊, Fatigue

◊Adverse events reported as serious in mantle cell lymphoma clinical trials
Algorithm applied for mantle cell lymphoma:

- Mantle cell lymphoma controlled Phase II study
    - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference in proportion between lenalidomide and control arm
    - All treatment-emergent grade 3 or 4 adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
    - All Serious treatment-emergent adverse events in ≥1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm
- Mantle cell lymphoma single arm Phase II study
    - All treatment-emergent adverse events with ≥ 5% of subjects
    - All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects
    - All Serious treatment-emergent adverse events reported in 2 or more subjects

Tabulated summary of post-marketing adverse reactions
In addition to the above adverse reactions identified from the pivotal clinical trials, the following table is derived from data gathered from post-marketing data.

Table 5: ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Rare Tumour lysis syndrome
Blood and Lymphatic System Disorders	Not known Acquired haemophilia	
Endocrine Disorders	Common Hyperthyroidism	
Respiratory, Thoracic and Mediastinal Disorders		Not Known Interstitial pneumonitis
Gastrointestinal Disorders		Not Known Pancreatitis, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)
Hepatobiliary Disorders	Not Known Acute hepatic failure, Hepatitis toxic, Cytolytic hepatitis, Cholestatic hepatitis, Mixed cytolytic/cholestatic hepatitis	Not Known Acute hepatic failure, Hepatitis toxic^
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome, Toxic epidermal necrolysis Not Known Leukocytoclastic vasculitis

7. DRUG INTERACTIONS

Results from human in vitro studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.
In vitro studies demonstrated that REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.
In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

7.1 Digoxin

When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

7.2 Warfarin

Co-administration of multiple dose REVLIMID (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

7.3 Concomitant Therapies That May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID [*see Warnings and Precautions (5.4)*].

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [*see Boxed Warnings and Contraindications (4.1)*]
Risk Summary
REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. REVLIMID is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the attending physician and Neopharm.

Animal data
In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral

lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.
Females of childbearing potential must use two reliable forms of contraception simultaneously for 4 weeks before therapy, during lenalidomide therapy and dose interruptions, and for 4 weeks following discontinuation of lenalidomide therapy, or continually abstain from reproductive heterosexual sexual intercourse. Because of the increased risk of VTE in patients with multiple myeloma taking lenalidomide and dexamethasone, and to a lesser extent patients with MDS taking lenalidomide monotherapy, and because there is an increased risk of VTE in patients taking combined oral contraceptive pills, physicians should discuss the risk/benefit of contraceptive methods with their patients.

8.2 Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric use

Revlimid should not be used in children and adolescents from birth to less than 18 years because of safety concerns.

8.4 Geriatric use

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 91 years of age.

- Newly diagnosed multiple myeloma

In patients with newly diagnosed multiple myeloma aged 75 years and older who received lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered.
In clinical trials of newly diagnosed multiple myeloma in transplant non eligible patients, lenalidomide combined therapy was less tolerated in patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75years.

- Multiple myeloma with at least one prior therapy

Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received REVLIMID/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of REVLIMID. No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs.16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

- Mantle cell lymphoma

For mantle cell lymphoma patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged 65 years or over compared with patients aged under 65 years of age.
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selectionand it would be prudent to monitor renal function.

8.5 Females of Reproductive Potential and Males

PLEASE REFER TO SECTION 5.2 "REPRODUCTIVE RISK AND SPECIAL PRESCRIBING REQUIREMENTS"

8.6 Renal Impairment

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis [*see Dosage and Administration (2.4)*].

8.7 Hepatic Impairment

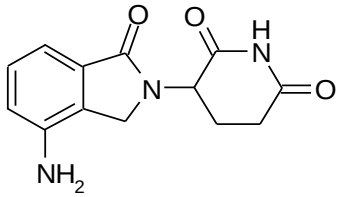
No dedicated study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

9. OVERDOSAGE

There is no specific experience in the management of lenalidomide overdose in patients; although in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.
In studies, the dose-limiting toxicity was essentially hematological. In the event of overdose, supportive care is advised.

10. DESCRIPTION

REVLIMID, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID is available in 2.5 mg, 5 mg, 7.5mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules for oral administration. Each hard capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg and 25 mg hard capsule shell contains gelatin, titanium dioxide and black ink. The 2.5 mg and 10 mg hard capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink. The 15 mg hard capsule shell contains gelatin, FD&C blue #2, titanium dioxide and black ink. The 20 mg hard capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

11. CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q) myelodysplastic syndromes *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

11.2 Pharmacodynamics

The effect of lenalidomide on the QTc interval was evaluated in 60 healthy male subjects in a randomized, thorough QT study with placebo and positive controls. At a dose two times the maximum recommended dose, lenalidomide does not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytoxic and immunomodulatory effects.

11.3 Pharmacokinetics

Absorption
Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of REVLIMID in patients with MM or MDS the maximum plasma concentrations occurred between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose. Multiple dosing at the recommended dose-regimen does not result in medicinal product accumulation.

Systemic exposure (AUC) of lenalidomide in MM and MDS patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects.

Administration of a single 25 mg dose of REVLIMID with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in C_{max}. In the trials where the efficacy and safety were established for REVLIMID, the medicinal product was administered without regard to food intake. REVLIMID can be administered with or without food.

Population pharmacokinetic analyses show that the oral absorption rate of lenalidomide in patients with MCL is similar to that observed in patients with MM or MDS.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism
Lenalidomide -undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

Elimination
Elimination is primarily renal. Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. 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.
The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.

Effect of Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg) has no clinically relevant effect on the multiple dose pharmacokinetics of REVLIMID (25 mg).

Specific Populations
Patients with Renal Impairment: The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant conditions. In this study, 5 patients with mild renal impairment (creatinine clearance 57-74 mL/min), 6 patients with moderate renal impairment (creatinine clearance 33-46 mL/min), 6 patients with severe renal impairment (creatinine clearance 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25-mg dose of REVLIMID. As a control group comparator, 7 healthy subjects of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also administered a single oral 25-mg dose of REVLIMID. As creatinine clearance decreased from mild to severe impairment, half-life increased and drug clearance decreased linearly. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of lenalidomide has an approximate 4.5-fold increase in half-life and an 80% decrease in drug clearance compared to healthy subjects. Approximately 40% of the administered dose was removed from the body during a single dialysis session.
In MM patients, those patients with mild renal impairment had an AUC 56% greater than those with normal renal function.

Adjustment of the starting dose of REVLIMID is recommended in patients with moderate or severe (CLcr < 60 mL/min) renal impairment and in patients on dialysis [*see Dosage and Administration (2.4)*].

Elderly Patients: No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide 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.

Patients with Hepatic Disease: Population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin >1 to ≤ 1.5 x ULN or AST > ULN) and show that mild hepatic impairment does not influence the disposition of lenalidomide. There are no data available for patients with moderate to severe hepatic impairment.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

Other Intrinsic Factors: Population pharmacokinetic analyses show that body weight (33-135 kg), gender, race, and type of hematological malignancies (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

12. NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with lenalidomide have not been conducted.
Lenalidomide was not mutagenic in the bacterial reverse mutation assay (Ames test) and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, or mutations at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times the human dose of 25 mg, based on body surface area) produced no parental toxicity and no adverse effects on fertility.

12. 2 Reproductive and Developmental Toxicity

Lenalidomide had an embryocidal effect in rabbits at a dose of 50 mg/kg (approximately 120 times the human dose of 10 mg based on body surface area).

In an embryofetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis at doses approximately 0.17 times the maximum recommended human dose (MRHD) of 25 mg, based on body surface area.

A pre- and post-natal development study in rats revealed few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring.

13. CLINICAL STUDIES

13.1 Newly diagnosed multiple myeloma

Lenalidomide has been evaluated in two phase III studies in newly diagnosed multiple myeloma.

Lenalidomide in combination with dexamethasone in patients who are not candidates for stem cell transplantation:

The safety and efficacy of lenalidomide was assessed in a Phase III, multicenter, randomized, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e., until progressive disease [Arm Rd] or for up to eighteen 28-day cycles [72 weeks, Arm Rd18]) to that of melphalan, prednisone and thalidomide (MPT) for a maximum of twelve 42-day cycles (72 weeks). Patients were randomized (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomization by age (≤75 versus >75 years), stage (ISS Stages I and II versus Stage III), and country.

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 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, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. 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, 9%

had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2, OS and DR where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 5:

Table 5: Summary of overall efficacy data

	Rd (N = 541)	**Rd18 (N = 540)**	**MPT (N = 542)**
Investigator-assessed PFS (months)			
Median[a] PFS time, months (95% CI)[b]	26.0 (20.7, 29.7)	21.0 (19.7, 22.4)	21.9 (19.8, 23.9)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.69 (0.59, 0.80); <0.001		
Rd vs Rd18	0.71 (0.61, 0.83); <0.001		
Rd18 vs MPT	0.99 (0.86, 1.14); <0.001		
PFS2[e] (months)			
Median[a] PFS time, months (95% CI)[b]	42.9 (38.1, 47.4)	40.0 (36.2, 44.2)	35.0 (30.4, 37.8)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.74 (0.63, 0.86); <0.001		
Rd vs Rd18	0.92 (0.78, 1.08); 0.316		
Rd18 vs MPT	0.80 (0.69, 0.93); 0.004		
Overall survival (months)			
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.75 (0.62, 0.90); 0.002		
Rd vs Rd18	0.91 (0.75, 1.09); 0.305		
Rd18 vs MPT	0.83 (0.69, 0.99); 0.034		
Follow-up (months)			
Median[f] (min, max): all patients	40.8 (0.0, 65.9)	40.1 (0.4, 65.7)	38.7 (0.0, 64.2)
Myeloma response[g] 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)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)
Duration of response (months)[h]			
Median[a] (95% CI)[b]	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

AMT = antimyeloma therapy; CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; IMWG = International Myeloma Working Group; IRAC = Independent Response Adjudication Committee; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for ≥ 18 cycles; SE = standard error; T = thalidomide; VGPR = very good partial response; vs = versus.

[a] The median is based on the Kaplan-Meier estimate.

[b] The 95% CI about the median.

[c] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.

[d] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.

[e] Exploratory endpoint (PFS2)

[f] The median is the univariate statistic without adjusting for censoring.

[g] Best assessment of adjudicated response during the treatment phase of the study (for definitions of each response category, Data cutoff date = 24 May 2013).
[h] data cut 24 May 2014

Lenalidomide in combination with melphalan and prednisone followed by maintenance monotherapy in patients not eligible for transplant

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

This study investigated the use of combination therapy of MPR (melphalan 0.18 mg/kg orally on days 1-4 of repeated 28-day cycles; prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles; and lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles) for induction therapy, up to 9 cycles. Patients who completed 9 cycles or who were unable to complete 9 cycles due to intolerance proceeded to maintenance monotherapy starting with lenalidomide 10 mg orally on days 1-21 of repeated 28-day cycles until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 459 patients were enrolled into the study, with 152 patients randomized to MPR+R, 153 patients randomized to MPR+p and 154 patients randomized to MPp+p. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms; notably, approximately 50% of the patients enrolled in each arm had the following characteristics; ISS Stage III, and creatinine clearance < 60 mL/min. The median age was 71 in the MPR+R and MPR+p arms and 72 in the MPp+p arm.

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 6:

Table 6: Summary of overall efficacy data

	MPR+R (N = 152)	**MPR+p (N = 153)**	**MPp +p (N = 154)**
Investigator-assessed PFS [g] (months)			
Median[a] PFS time, months (95% CI)	27.4 (21.3, 35.0)	14.3 (13.2, 15.7)	13.1 (12.0, 14.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.37 (0.27, 0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35, 0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60, 1.01); 0.059		
PFS2 [g] (months) [¤]			
Median[a] PFS time, months (95% CI)	39.7 (29.2, 48.4)	27.8 (23.1, 33.1)	28.8 (24.3, 33.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.70 (0.54, 0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59, 1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71, 1.19); 0.051		

	MPR+R (N = 152)	MPR+p (N = 153)	MPp +p (N = 154)
Overall survival (months)			
Median[a] OS time, months (95% CI)	55.9 (49.1, 67.5)	51.9 (43.1, 60.6)	53.9 (47.3, 64.2)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.95 (0.70, 1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65, 1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79, 1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8, 73.8)	46.3 (0.5, 71.9)	50.4 (0.5, 73.3)
Investigator-assessed Myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable (NE)	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed Duration of response (CR+PR) □ (months)			
Median[a] (95% CI)	26.5 (19.4, 35.8)	12.4 (11.2, 13.9)	12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone;
PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.
[a] The median is based on the Kaplan-Meier estimate
[b]PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomization to start of 3rd line antimyeloma therapy (AMT) or death for all randomized patients

Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, Phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

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

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

13.2 Multiple myeloma with at least one prior therapy

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of REVLIMID. These multicenter, multinational, double-blind, placebo-controlled studies compared REVLIMID plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone in patients with multiple myeloma who had received at least one prior treatment. These studies enrolled patients with absolute neutrophil counts (ANC) $\geq 1000/mm^3$, platelet counts $\geq 75{,}000/mm^3$, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL.

In both studies, patients in the REVLIMID/dexamethasone group took 25 mg of REVLIMID orally once daily on Days 1 to 21 and a matching placebo hard capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took 1 placebo hard 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 findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity [*see Dosage and Administration (2.2)*].
Table 7 summarizes the baseline patient and disease characteristics in the two studies. In both studies, baseline demographic and disease-related characteristics were comparable between the REVLIMID/dexamethasone and placebo/dexamethasone groups.

Table 7: Baseline Demographic and Disease-Related Characteristics – Studies 1 and 2

	Study 1		**Study 2**	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
Patient Characteristics				
Age (years)				
Median	64	62	63	64
Min, Max	36, 86	37, 85	33, 84	40, 82
Sex				
Male	106 (60%)	104 (59%)	104 (59%)	103 (59%)
Female	71 (40%)	72 (41%)	72 (41%)	72 (41%)
Race/Ethnicity				
White	141(80%)	148 (84%)	172 (98%)	175(100%)
Other	36 (20%)	28 (16%)	4 (2%)	0 (0%)
ECOG Performance Status 0-1	157 (89%)	168 (95%)	150 (85%)	144 (82%)
Disease Characteristics				
Multiple Myeloma Stage (Durie-Salmon)				
I	3%	3%	6%	5%
II	32%	31%	28%	33%
III	64%	66%	65%	63%

B2-microglobulin (mg/L) ≤ 2.5 mg/L > 2.5 mg/L	52 (29%) 125 (71%)	51 (29%) 125 (71%)	51 (29%) 125 (71%)	48 (27%) 127 (73%)
Number of Prior Therapies				
1 ≥ 2	38% 62%	38% 62%	32% 68%	33% 67%
Types of Prior Therapies				
Stem Cell Transplantation	62%	61%	55%	54%
Thalidomide	42%	46%	30%	38%
Dexamethasone	81%	71%	66%	69%
Bortezomib	11%	11%	5%	4%
Melphalan	33%	31%	56%	52%
Doxorubicin	55%	51%	56%	57%

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease.

Preplanned interim analyses of both studies showed that the combination of REVLIMID/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the REVLIMID/dexamethasone combination. For both studies, the extended follow-up survival data with crossovers were analyzed. In study 1, the median survival time was 39.4 months (95%CI: 32.9, 47.4) in REVLIMID/dexamethasone group and 31.6 months (95%CI: 24.1, 40.9) in placebo/dexamethasone group, with a hazard ratio of 0.79 (95% CI: 0.61-1.03). In study 2, the median survival time was 37.5 months (95%CI: 29.9, 46.6) in REVLIMID/dexamethasone group and 30.8 months (95%CI: 23.5, 40.3) in placebo/dexamethasone group, with a hazard ratio of 0.86 (95% CI: 0.65-1.14).

Table 8: TTP Results in Study 1 and Study 2

	Study 1		**Study 2**	
	REVLIMID/Dex N=177	**Placebo/Dex N=176**	**REVLIMID/Dex N=176**	**Placebo/Dex N=175**
TTP				
Events n (%)	73 (41)	120 (68)	68 (39)	130 (74)
Median TTP in months [95% CI]	13.9 [9.5, 18.5]	4.7 [3.7, 4.9]	12.1 [9.5, NE]	4.7 [3.8, 4.8]
Hazard Ratio [95% CI]	0.285 [0.210, 0.386]		0.324 [0.240, 0.438]	
Log-rank Test p-value 3	<0.001		<0.001	
Response				

Complete Response (CR) n (%)	23 (13)	1 (1)	27 (15)	7 (4)
Partial Response (RR/PR) n (%)	84 (48)	33 (19)	77 (44)	34 (19)
Overall Response n (%)	107 (61)	34 (19)	104 (59)	41 (23)
p-value	<0.001		<0.001	
Odds Ratio [95% CI]	6.38 [3.95, 10.32]		4.72 [2.98, 7.49]	

Figure 1: Kaplan-Meier Estimate of Time to Progression — Study 1

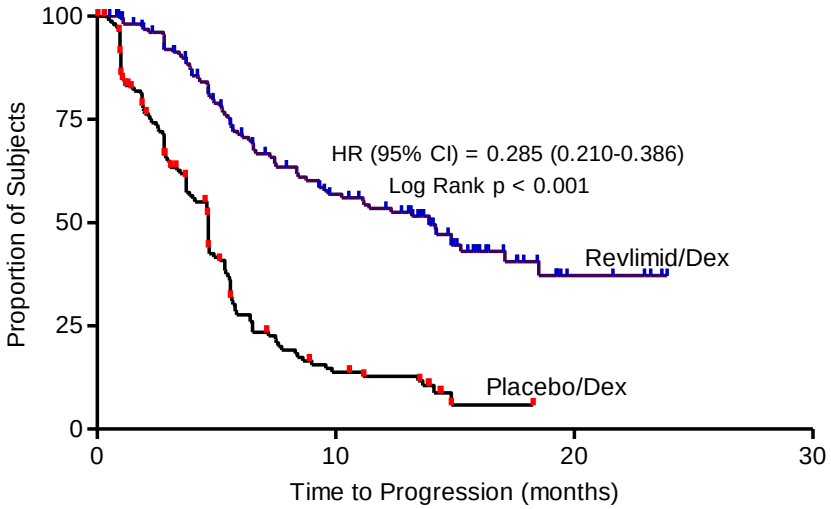
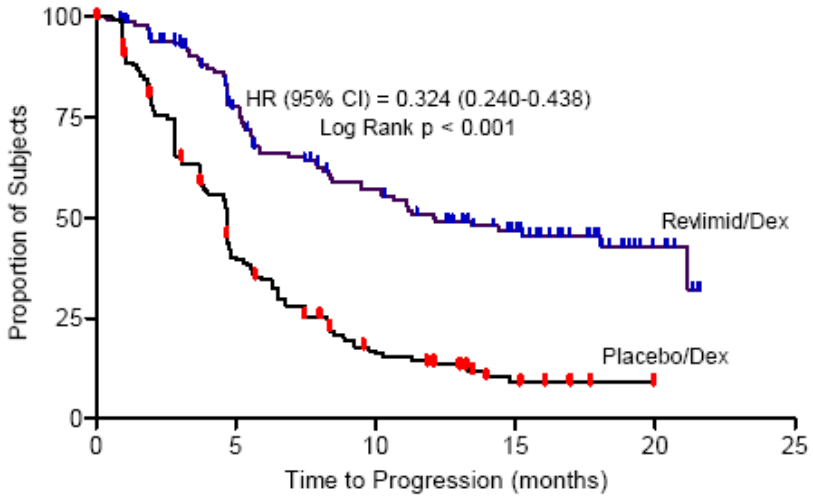


Figure 2: Kaplan-Meier Estimate of Time to Progression — Study 2



13.3 Myelodysplastic Syndromes (MDS) with a Deletion 5q Cytogenetic Abnormality

The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anemia in low- or intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity [*Dosage and Administration (2.3)*].
This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC transfusion dependence was defined as having received ≥ 2 units of RBCs within 8 weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts (ANC) ≥ 500/mm^3, platelet counts ≥ 50,000/mm^3, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3 x upper limit of normal (ULN), and serum direct bilirubin ≤ 2 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. Baseline patient and disease-related characteristics are summarized in Table 9.

Table 9: Baseline Demographic and Disease-Related Characteristics in the MDS Study

	Overall (N=148)	
Age (years)		
Median	71.0	
Min, Max	37.0, 95.0	
Gender	**n**	**(%)**
Male	51	(34.5)
Female	97	(65.5)
Race	**n**	**(%)**
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1, 20.7	
Del 5 (q31-33) Cytogenetic Abnormality	**n**	**(%)**
Yes	148	(100.0)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	**n**	**(%)**
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	65	(43.9)
Intermediate-2 (1.5-2.0)	6	(4.1)
High (≥2.5)	2	(1.4)
Missing	20	(13.5)
FAB Classification [b] from central review	**n**	**(%)**
RA	77	(52.0)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2.0)

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0),

Intermediate-2 (combined score = 1.5 to 2.0), High (combined score ≥ 2.5); Combined score =

(Marrow blast score + Karyotype score + Cytopenia score)

[b] French-American-British (FAB) classification of MDS.

The frequency of RBC transfusion independence was assessed using criteria modified from the International Working Group (IWG) response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (8 weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) patients (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to >67 weeks). Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study.

RBC transfusion independence rates were unaffected by age or gender.

The dose of REVLIMID was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).

13.4 Mantle Cell Lymphoma

The efficacy and safety of lenalidomide were evaluated in patients with mantle cell lymphoma in a phase II, multicenter, randomized open-label study versus single agent of investigator's choice in patients who were refractory to their last regimen or had relapsed one to three times (Study MCL-002).

Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomized 2:1 to the lenalidomide or the control arm. The investigator's choice treatment was selected before randomization 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 (D1 to D21) 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 baseline demographic were comparable between the lenalidomide arm and control arm. Both patient populations presented a median age of 68.5 years with comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number of prior therapies.

The primary efficacy endpoint in Study MCL-002 was progression-free survival (PFS).

The efficacy results for the Intent-to-Treat (ITT) population were assessed by the Independent Review Committee (IRC), and are presented in the table below.

Table 8: Summary of efficacy results – study MCL-002, intent-to-treat population

	Lenalidomide Arm N = 170	**Control Arm** N = 84
PFS		
PFS, median[a] [95% CI][b] (weeks)	37.6 [24.0, 52.6]	22.7 [15.9, 30.1]
Sequential HR [95% CI][e]	0.61 [0.44, 0.84]	
Sequential log-rank test, p-value[e]	0.004	
Response[a], n (%)		
Complete response (CR)	8 (4.7)	0 (0.0)
Partial response (PR)	60 (35.3)	9 (10.7)
Stable disease (SD)[b]	50 (29.4)	44 (52.4)
Progressive disease (PD)	34 (20.0)	26 (31.0)
Not done/Missing	18 (10.6)	5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][c]	68 (40.0) [32.58, 47.78]	9 (10.7)[d] [5.02, 19.37]
p-value[e]	< 0.001	
CRR (CR, CRu), n (%) [95% CI][c]	8 (4.7) [2.05, 9.06]	0 (0.0) [95.70, 100.00]
p-value[e]	0.043	
Duration of Response, median[a] [95% CI] (weeks)	69.6 [41.1, 86.7]	45.1 [36.3, 80.9]
Overall Survival		
HR [95% CI][c]	0.89 [0.62, 1.28]	
Log-rank test, p-value	0.520	

CI = confidence interval; CRR = complete response rate; CR = complete response; CRu = complete response unconfirmed; DMC = Data Monitoring Committee; ITT = intent-to-treat; HR = hazard ratio; KM = Kaplan-Meier; MIPI = Mantle Cell Lymphoma International Prognostic Index; NA = not applicable; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR= partial response; SCT = stem cell transplantation; SD = stable disease; SE = standard error.

[a] The median was based on the KM estimate.

[b] Range was calculated as 95% CIs about the median survival time.

[c] The mean and median are the univariate statistics without adjusting for censoring.

[d] The stratification variables included time from diagnosis to first dose (< 3 years and ≥ 3 years), time from last prior systemic anti-lymphoma therapy to first dose (< 6 months and ≥ 6 months), prior SCT (yes or no), and MIPI at baseline (low, intermediate, and high risk).

[e] Sequential test was based on a weighted mean of a log-rank test statistic using the unstratified log-rank test for sample size increase and the unstratified log-rank test of the primary analysis. The weights are based on observed events at the time the third DMC meeting was held and based on the difference between observed and expected events at the time of the primary analysis. The associated sequential HR and the corresponding 95% CI are presented.

In study MCL-002 in the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. In patients with high tumour burden, corresponding figures were 16/81 (20%) and 2/28 (7%).

14. REFERENCES

OSHA Hazardous Drugs. *OSHA* [Accessed on 29 January 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

15. HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

White and blue-green opaque hard capsules imprinted “REV” on one half and “2.5 mg” on the other half in black ink:
2.5 mg blisters of 21
White opaque hard capsules imprinted “REV” on one half and “5 mg” on the other half in black ink:
5 mg blisters of 215 mg bottles of 28
5 mg bottles of 100
Pale yellow/white hard capsules marked “REV 7.5 mg”
7.5 mg blisters of 21 hard capsules.
Blue/green and pale yellow opaque hard capsules imprinted “REV” on one half and “10 mg” on the other half in black ink:
10 mg blisters of 21
10 mg bottles of 28
10 mg bottles of 100
Powder blue and white opaque hard capsules imprinted “REV” on one half and “15 mg” on the other half in black ink:
15 mg blisters of 21
15 mg bottles of 21
15 mg bottles of 100
Powder blue and blue-green opaque hard capsules imprinted “REV” on one half and “20 mg” on the other half in black ink.
20 mg blisters of 21
White opaque hard capsules imprinted “REV” on one half and “25 mg” on the other half in black ink:
25 g blisters of 21
25 g bottles of 21
25 g bottles of 100

15.2 Storage

DO NOT STORE ABOVE 25°C.

15.2 Handling and Disposal

Care should be exercised in the handling of REVLIMID. REVLIMID hard capsules should not be opened or crushed. If powder from REVLIMID contacts the skin, wash the skin immediately and thoroughly with soap and water. If REVLIMID contacts the mucous membranes, flush thoroughly with water.
Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published.[1]
Dispense no more than a 28-day supply.

Registration No.
Revlimid 2.5mg: 151-24-33894-00, 151-24-33894-01, 151-24-33894-02, 151-24-33894-03
Revlimid 5mg: 140-45-31660-00, 140-45-31660-11, 140-45-31660-12, 140-45-31660-14, 140-45-31160-15, 140-45-31160-16
Revlimid 7.5mg: 151-25-33896-00, 151-25-33896-01, 151-25-33896-02, 151-25-33896-03
Revlimid 10mg: 140-46-31661-11, 140-46-31661-12, 140-46-31661-14, 140-46-31661-15,

140-46-31661-16
Revlimid 15mg: 140-47-31662-00, 140-47-31662-11, 140-47-31662-12, 140-47-31662-14, 140-47-31662-15, 140-47-31662-16
Revlimid 20mg: 151-26-33965-00, 151-26-33965-01, 151-26-33965-02, 151-26-33965-03, 151-26-33965-04
Revlimid 25mg: 140-48-31663-00, 140-48-31663-11, 140-48-31663-12, 140-48-31663-14, 140-48-31663-15, 140-48-31663-16

Manufacturers
Celgene International Sarl, Switzerland for Celgene Europe Limited, Stockley Park, Uxbridge, UK.
Celgene Corporation, Summit NJ, USA.

Registration Holder
Neopharm Scientific Ltd. P.O.B 7063, Petach Tiqva 49170

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