Healthcare Professional Brochure

Revlimid®

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Introduction

Revlimid® is an immunomodulating medicinal product.

Two Phase III clinical studies assessed lenalidomide maintenance in patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (ASCT) was assessed in (CALGB 100104 and IFM 2005-02).

In Study CALGB 100104, patients were randomised 1:1 within 90 to 100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on Days 1 to 28 of repeated 28-day cycles (increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity), and treatment was continued until disease progression.

The results of progression free survival (PFS) at unblinding (cut-off of 17 December 2009) showed a 62% reduction in risk of disease progression or death favoring lenalidomide over placebo. The Hazard Ratio was 0.38 (95% CI 0.27, 0.54; p <0.001). The median overall PFS was 33.9 months (95% CI not evaluable [NE], NE) in the lenalidomide arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm. The updated PFS, using a cut-off of 01 February 2016, continued to show a PFS advantage for lenalidomide (Hazard Ratio = 0.61; p <0.001).

In Study IFM 2005-02, patients who had undergone ASCT and had achieved at least a stable disease response at the time of haematologic recovery were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on Days 1 to 28 of repeated 28-day cycles increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity) following 2 courses of lenalidomide consolidation (25 mg/day, Days 1 to 21 of a 28-day cycle). Treatment was to be continued until disease progression. The study was unblinded upon the recommendations of the data monitoring committee after surpassing the threshold for a preplanned interim analysis of PFS. After unblinding, patients receiving placebo were not crossed over to lenalidomide therapy prior to progressive disease. The lenalidomide arm was discontinued, as a proactive safety measure, after observing an imbalance of SPM. The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 07 July 2010 (31.4 months follow-up) showed a 48% reduction in risk of disease progression or death favoring lenalidomide over placebo. The Hazard Ratio was 0.52 (95% CI 0.41, 0.66; p <0.001). The median overall PFS was 40.1 months (95% CI 35.7, 42.4) in the lenalidomide arm versus 22.8 months (95% CI 20.7, 27.4) in the placebo arm. The updated PFS, using a cut-off of 01 February 2016 (96.7 months follow-up) continued to show a PFS advantage for lenalidomide (Hazard Ratio = 0.57; p <0.001).

A Phase III clinical study in newly diagnosed multiple myeloma (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). The study showed a

statistically significant prolongation of progression-free survival (PFS) benefit in patients receiving Rd compared to MPT. The Hazard Ratio was 0.69 (p <0.001),.
Another Phase III study in newly diagnosed multiple myeloma (MM-015) was conducted to evaluate the safety and efficacy of 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.
The study showed a statistically significant prolongation of progression free survival (PFS) benefit in patients receiving MPR+R compared to MPp+p (melphalan, prednisone, placebo + placebo maintenance). The Hazard Ratio was 0.37 (p <0.001).*

In Phase III clinical studies in multiple myeloma with at least one prior therapy, the median time to progression (TTP) was 60.1 weeks in patients treated with lenalidomide/dexamethasone versus 20.1 weeks in patients treated with placebo/dexamethasone. The median progression free survival was 48.1 weeks in patients treated with lenalidomide/dexamethasone versus 20.0 weeks in patients treated with placebo/dexamethasone.*

In a Phase III clinical study in myelodysplastic syndromes (MDS-004), a significant larger proportion of patients achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms, but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL*.

In a phase II study of lenalidomide (N=170) versus single agent of investigator's choice of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine (N=84) in patients with mantle cell lymphoma (MCL) who were refractory to their last regimen or had relapsed one to three times (Study MCL-002), median PFS was significantly improved for lenalidomide versus investigator's choice (37.6 versus 22.7 weeks; Hazard Ratio = 0.61, p = 0.004).*

*text according to SmPC

- Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
  AND
- Revlimid® as combination therapy is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant
  AND

- Revlimid® in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy
  AND
- Revlimid® as monotherapy is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.
  AND
- Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

- Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic substance that causes severe life-threatening birth defects. An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4mg/kg/day. Findings from this study showed that lenalidomide produced malformations (short limbs, bent fingers/toes, wrist and/or tail, supernumerary or absent fingers/toes) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study. If Revlimid® is taken during pregnancy, a teratogenic effect can be expected. Therefore Revlimid® is contraindicated in pregnancy and in women of child bearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) described in this brochure are carried out.

- All men and all women of childbearing potential should undergo counselling of the need to avoid pregnancy. Treatment Initiation Forms are provided for this purpose with this Kit. These forms should be signed by both physician and patient; one copy retained by the patient and the other being retained in the patients records.

- Patients should be capable of complying with the requirements of safe use of Revlimid®.

- Patients must be provided with appropriate patient educational brochure and a copy of the Treatment Initiation Form.

- This document sets out the key points relating to the safe use of Revlimid®. For further information, please see the enclosed Summary of Product Characteristics.

- Local country specific arrangements about enrolment of patients with MDS in the MDS PASS according to the national implementation of the MDS PASS as agreed on by the National Competent Authority: *The MDS PASS will not be implemented in Malta, as agreed on with the Maltese Medicines Agency.*

Safety Advice relevant to all patients

1. Myelosuppression

- Neutropenia and thrombocytopenia are the major dose limiting toxicities

    - A complete blood count, including white blood count monitoring with differential count, platelet count, haemoglobin and haematocrit should be performed at baseline and every week for the first 8 weeks of treatment and then monthly thereafter to monitor for cytopenias. In mantle cell lymphoma patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then at the start of each cycle. A dose reduction may be required. In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

Newly diagnosed multiple myeloma patients who have undergone ASCT treated with lenalidomide maintenance

- The adverse reactions from CALGB 100104 included events reported post-high dose melphalan and ASCT (HDM/ASCT) as well as events from the maintenance treatment period. A second analysis identified events that occurred after the start of maintenance treatment. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

- Overall, grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reductions may be required.
- Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, 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 patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone

- The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 4 neutropenia (8.5% in Rd and Rd18, compared with 15% in MPT). Grade 4 febrile neutropenia was observed infrequently (0.6% compared with 0.7% in MPT).

- The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a decreased incidence of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18 compared to 11% in MPT).

Newly diagnosed multiple myeloma patients who are not eligible for transplant treated with lenalidomide in combination with melphalan and prednisone

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

- The combination of lenalidomide with melphalan and prednisone in newly diagnosed 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).

Multiple myeloma patients with at least one prior therapy

- The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with an incidence of grade 4 neutropenia of 5.1% compared with 0.6% in placebo/dexamethasone-treated patients. Grade 4 febrile neutropenia episodes were observed infrequently in 0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients.

- The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

Myelodysplastic syndromes patients

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

Mantle cell lymphoma patients

- In mantle cell lymphoma patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the Phase II study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm.

1.1 Newly diagnosed multiple myeloma

1.1.1. Lenalidomide maintenance in patients who have undergone ASCT

- Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

- The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on Days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

  - *Dose reduction steps*

	Starting dose (10 mg)	If dose increased (15 mg)[a]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (Days 1 to 21 every 28 days)	5 mg
Dose level -3	Not applicable	5 mg (Days 1 to 21 every 28 days)
	Do not dose below 5 mg (Days 1 to 21 every 28 days)	

[a] After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

  - *Thrombocytopenia*

When platelets	Recommended course
Fall to < 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -1 once daily
For each subsequent drop below 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily

  - *Neutropenia*

When neutrophils	Recommended course[a]
Fall to < 0.5 x 10^9/L Return to ≥ 0.5 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L Return to ≥ 0.5 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose

When neutrophils	Recommended course[a]
	level once daily

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

1.1.2. 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.

- The recommended starting dose of lenalidomide is 25mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of low dose dexamethasone is 40mg 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 10mg once daily.

<u>Recommended dose adjustments during treatment and restart of treatment</u>
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	40mg
Dose level -1	20 mg	20mg
Dose level -2	15 mg	12mg
Dose level -3	10 mg	8mg
Dose level- 4	5 mg	4mg
Dose level -5	2.5mg	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 physician should consider the use of growth factors in patient management.

- If the dose of lenalidomide was reduced for a hematologic dose limiting toxicity (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).

1.1.3. 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 Absolute Neutrophil Counts (ANC) is < 1.5 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

- 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.

<u>Recommended dose adjustments during treatment and restart of treatment</u>
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]	0.18mg/kg	2mg/kg
Dose level -1	7.5 mg	0.14 mg/kg	1mg/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 Return to ≥ 25 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide and melphalan at Dose Level -1
For each subsequent drop below 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose Level -2 or -3) once daily.

Neutropenia

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

[a] *If the subject has not receiving G-CSF therapy, initiate G-CSF therapy. On Day 1 of next cycle, continue GCSF 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 physician should consider the use of growth factors in patient management.

1.2 Multiple Myeloma with at least one prior therapy

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

- The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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

Dose reduction steps

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

Thrombocytopenia

When platelets	Recommended course
First fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at Dose level -1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily. Do not dose below 5 mg once daily.

Neutropenia

When neutrophils	Recommended course

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

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

1.3 Myelodysplastic Syndromes

- Lenalidomide treatment must not be started if the Absolute Neutrophil Count (ANC) < 0.5 x 10^9/L and/or platelet count < 25 x 10^9/L.

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

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

- *Dose reduction steps*

Starting dose	10 mg once daily on days 1-21 every 28 days
Dose level -1	5.0 mg once daily on days 1-28 every 28 days
Dose level -2	2.5 mg once daily on days 1-28 every 28 days
Dose level -3	2.5 mg every other day 1-28 every 28 days

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

Thrombocytopenia

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

Neutropenia

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

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.

1.4 Mantle cell lymphoma

The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1 to 21 of repeated 28-day cycles.

- *Dose reduction steps*

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

[a] In countries where the 2.5 mg capsule is available.

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 50 x 10^9/L	Interrupt lenalidomide 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 lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥ 60 x 10^9/L	Resume lenalidomide 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 associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥ 1 x 10^9/L	Resume lenalidomide 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 lenalidomide treatment
Returns to ≥ 1 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -2, -3, -4, -5). Do not dose below dose level -5

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2. <u>Recommended dose adjustments for other toxicities</u>

- 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 is suspected, and should not be resumed following discontinuation from these reactions.

<u>3. Venous and arterial thromboembolism</u>

- In patients with multiple myeloma, the combination of Revlimid® and dexamethasone is associated with an increased risk of venous and arterial thromboembolic events (predominantly deep vein thrombosis (DVT), pulmonary

embolism (PE), myocardial infarctions and cerebrovascular events. 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 and mantle cell lymphoma.

- In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma.

- Action should be taken to try to minimize all modifiable risk factors for thromboembolic events (e.g. smoking cessation, control of hypertension and hyperlipidaemia). Patients with known risk factors for thromboembolism including previous thrombosis should be closely monitored.

- Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase the thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

- Prophylactic antithrombotic medications should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

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

- Patients should be advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

4. Patients with renal failure

- Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment.

- No dose adjustments are required for patients with mild renal impairment and multiple myeloma or myelodysplastic syndromes or mantle cell lymphoma. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no Phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

4.1 Multiple myeloma

Renal function (CLcr)	**Dose adjustment** (Days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5mg once daily. On dialysis days, the dose should be administered following dialysis.

[1]*The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.
[2] In countries where the 7.5 mg capsule is available.

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

4.2 Myelodysplastic syndromes

Renal function (CLcr)	**Dose adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 mL/min, not requiring	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day

dialysis)		cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

4.3 Mantle cell lymphoma

Renal function (CLcr)	**Dose adjustment** (Days 1-21 of repeated 28- day cycles)
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis.

[1] The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.
[2] In countries where the 7.5 mg capsule is available.

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

5. Hepatic Impairment

Population pharmacokinetic analyses included patients with mild hepatic impairment (N=16, total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicate that mild hepatic impairment does not influence lenalidomide clearance (exposure in plasma). There are no data available for patients with moderate to severe hepatic impairment.

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

6. Peripheral neuropathy

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

7. Tumour Flare Reaction

Tumour flare reaction (TFR) has commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. The patients at risk of 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 and appropriate precautions taken.

8. Allergic Reactions

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

9. Severe Skin Reactions

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

10. Second primary malignancies

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

In clinical trials of newly diagnosed multiple myeloma 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 (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).

The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterised, it should be kept in mind when considering and using Revlimid in this setting.

The incidence rate of haematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not exposed to lenalidomide after ASCT).

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with Revlimid® either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated

11. Progression to acute myeloid leukaemia in low- and int-1-risk MDS

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a combined analysis of two clinical trials of Revlimid® in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality.

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

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

Progression to other malignancies in mantle cell lymphoma
In mantle cell lymphoma, AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are potential risks.

12. 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 in patients with NDMM who are not eligible for transplant, and with lenalidomide maintenance compared to placebo in patients with NDMM who had undergone ASCT. 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 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.

13. Hepatic Disorders

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors. Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions 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 medicinal products known to be associated with liver dysfunction.

14. Disposal of unwanted medicine

Patients should be advised never to give Revlimid® to another person and to return any unused capsules to their pharmacist at the end of the treatment.

15. Blood donation

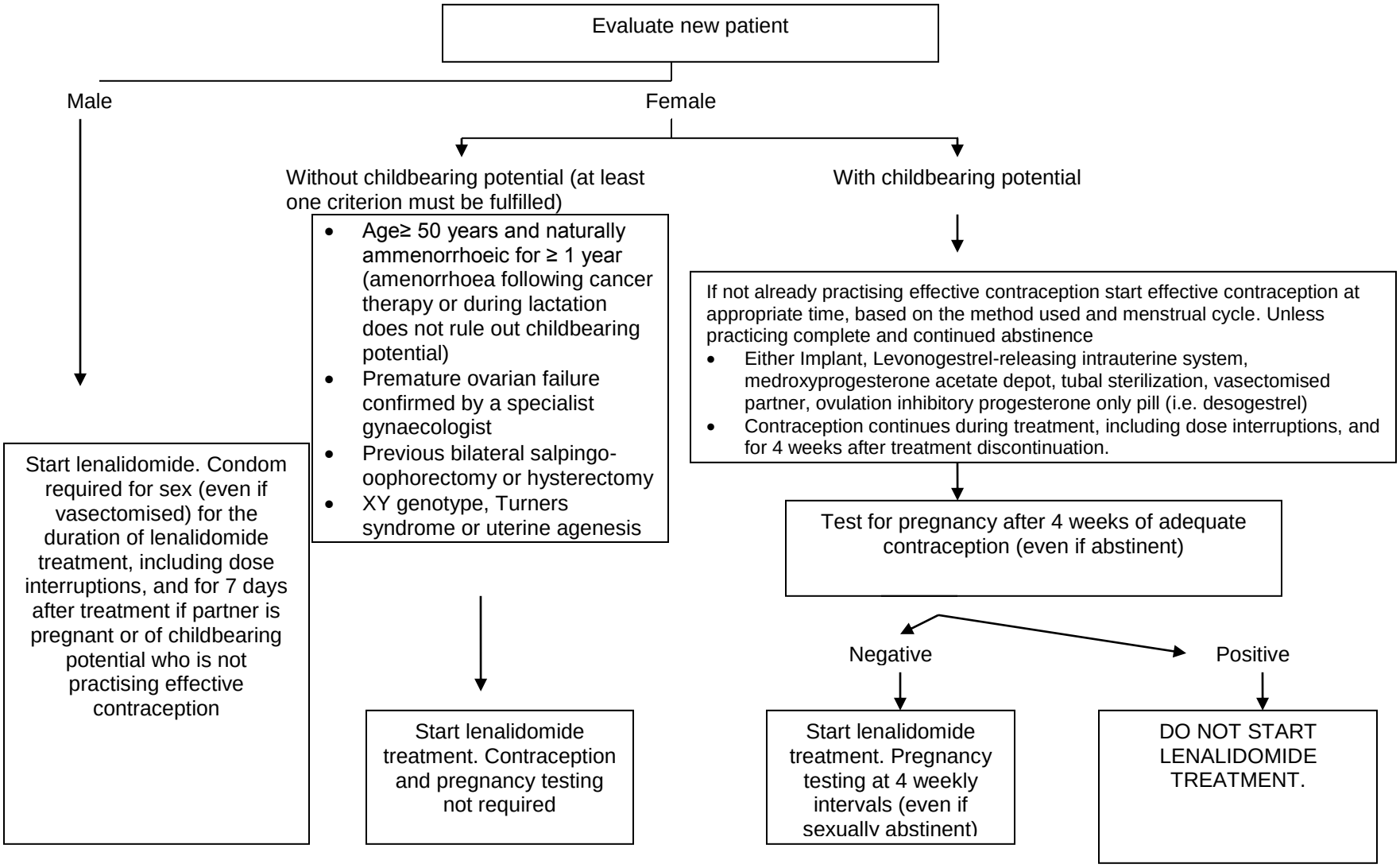
Patients should not donate blood during treatment and for 7 days after cessation of treatment with Revlimid®.

Pregnancy Prevention Programme

- Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance. Lenalidomide induced malformations in monkeys similar to those described for thalidomide. If Revlimid® is taken in pregnancy, a teratogenic effect in humans is expected.

- Revlimid® is therefore contraindicated in pregnancy. It is also contraindicated in women of childbearing potential unless all the conditions of the Revlimid® Pregnancy Prevention Programme are met.

- The Pregnancy Prevention Programme is set out in the following Algorithm



- The following are considered to not have childbearing potential.
    - Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
    - Confirmed premature ovarian failure if confirmed by specialist gynaecologist.
    - Previous bilateral salpingo-oophorectomy, or hysterectomy
    - XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

You are advised to refer your patient for a gynaecological opinion if you are unsure whether or not she meets these criteria.

Safety Advice for Women of Childbearing Potential

- In view of the expected teratogenic risk of Revlimid®, foetal exposure should be avoided

- Women of childbearing potential (even if they have amenorrhoea) must:
    - use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after Revlimid® therapy, and even in case of dose interruption.
    - commit to absolute and continuous sexual abstinence

    AND
    - Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25m IU/mL) once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy (this includes dose interruptions) and 4 weeks after the end of therapy (unless confirmed tubal sterilisation). This includes those women of childbearing potential who confirm absolute and continuous sexual abstinence.

- Patients should be advised to inform the physician prescribing her contraception about the Revlimid® treatment.

- Patients should be advised to inform you if a change or stop of method of contraception is needed.

If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:
- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal Sterilisation

- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, and to a lesser extent in patients with myelodysplastic syndromes taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

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

- Your patient should be advised that if a pregnancy does occur whilst she is receiving Revlimid®, she must stop treatment immediately and inform her physician immediately.

Safety Advice for Men

- In view of the expected teratogenic risk of Revlimid®, foetal exposure should be avoided

- Inform your patient which are the effective contraceptive methods that his female partner can use.

- Revlimid® is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for 7 days after cessation of treatment if their partner is pregnant or of childbearing potential who is not using effective contraception and even if the male patient has undergone vasectomy.

- Patients should be instructed that if their partner becomes pregnant whilst he is taking Revlimid® or shortly after he has stopped taking Revlimid® he should inform his treating doctor immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice.

Requirements in the event of a suspected pregnancy

- Stop treatment immediately, if female patient.

- Refer patient to a physician specialised or experienced in teratology for evaluation and advice.
- Notify AM Mangion Ltd of all such occurrences (suspected or confirmed pregnancy or foetal exposure) using the Pregnancy Capture Form is included in this pack:

AM Mangion Ltd.
Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
Tel: +356 23976333
Fax: +356 239 76123
Email: pv@ammangion.com

AM Mangion Ltd will wish to follow-up with you the progress of all pregnancies.

Reporting of Adverse Reactions
Suspected adverse reactions and medication errors should be reported at
ADR Reporting, The Medicines Authority, Post-Licensing Directorate,
Sir Temi Zammit Buildings, Malta Life Sciences Park,
San Gwann SGN 3000, Malta

Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

OR

ADR Reporting: www.medicinesauthority.gov.mt/adrportal

Communication of Safety Information to other Physicians
It is important that other physicians, for example the patient's general practitioner, who may care for the patient for other conditions are aware of the potential risks of lenalidomide. To assist in this communication, the pack includes a template letter to other treating physicians containing the key safety information for lenalidomide. This wording can be used in communications and between you and other physicians involved in the patient care.

Distribution mechanism for lenalidomide supply
Celgene has implemented a controlled distribution system in order to ensure prevention of foetal exposure to lenalidomide. Prior to treating a patient with lenalidomide, it is required that the treating physician and the patient sign a Treatment Initiation Form to confirm that the benefits and risks of lenalidomide therapy have been explained and understood and that the requirements of the Pregnancy Prevention Programme will be complied with. One copy of this form should be given to the patient and the other should be retained in the patient file. In addition, patients should be provided with the relevant patient information booklet in Maltese or English.

Patient Cards to document childbearing status are contained within the Healthcare Professional Kit. The Patient Cards must be signed to confirm counselling has taken place. For women of childbearing potential, the Patient Card will also document the date and results of the monthly pregnancy test. The Patient Card must be completed and a copy provided to the patient. The pharmacist will be required to verify the correct completion of the patient card for each female patient prior to each dispense of lenalidomide.

For those patients who are women of childbearing potential, prescriptions should be limited to one month supply. Dispensing of lenalidomide to women of childbearing potential should only occur within a maximum of 7 days of either the prescription date or the last pregnancy test date, whichever comes first.

Contact Details

For information and questions on the risk management of Celgene's products, and the Pregnancy Prevention Programme,

AM Mangion Ltd.
Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
Tel : +356 23976333
Fax: +356 239 76123
Email : pv@ammangion.com

