Zelvina® (Lenalidomide) Information for Healthcare professionals Brochure

Approved by the Malta Medicines Authority on the 02nd of February 2024.

Lenalidomide as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myelomas who have undergone autologous stem cell transplantation.

AND

Lenalidomide as combination therapy is indicated for the treatment of adult patients with previously untreated multiple myelomas who are not eligible for transplant. AND • Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

AND

Lenalidomide as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnom1ality when other therapeutic options are insufficient or inadequate.

AND

Lenalidomide 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 bit1h defects. An embryo foetal development study has been conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Findings from this study showed that lenalidomide produced malfunctions (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study. If Lenalidomide is taken during pregnancy, a teratogenic effect can be expected. Therefore, Lenalidomide is contraindicated in pregnancy and in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme described in tl1is brochure are carried out.

All men and all women of childbearing potential should undergo counselling of the need to avoid pregnancy (checklists for counselling are provided with this pack)

Patients should be capable of complying with the requirements of safe use of Lenalidomide.

Patients must be provided with appropriate patient educational brochure and patient card.

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 lenalidomide treatment and monthly thereafter to monitor for cytopenia's. 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 am1s compared to the placebo maintenance am1s 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'Yo vs. 0.5% [0.4% vs. 0.5% after the start of maintenm1ce 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 am1s 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 epistaxis, 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 lower frequency of grade 4 neutropenia (8.5% in Rd and Rdl8, compared with MPT [15%]). Grade 4 febrile neutropenia was observed infrequently (0.6% in Rd and Rd18 compared with 0.7% in MPT).

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18 compared with MPT [11.1%]).

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 frequency of grade 4 neutropenia (34.1% in MPR+RJMPR+p compared with 7.8% in MPp+p). There was a higher frequency of grade 4 febrile neutropenia observed (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 frequency of grade 3 and grade 4thrombocytopenia (40.4% in MPR+RJMPR+p, compared with MPp+p (13.7%]). Multiple myeloma patients with a least one prior therapy

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 lll 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 109 /L, and/or platelet counts are 75 x 109 /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 reductions

	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)	

After 3 cycles of maintenance, the dose can be increased to 15 mg orally once daily in tolerated.

Thrombocytopenia

When platelets	Recommended course
Falls to <30 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥50 x 10^9/L	Resume lenalidomide at dose level-1 once daily
For each subsequent drop below 30X10^9/L	Interrupt lenalidomide treatment
Return to ≥30X10^9/L	Resume lenalidomide at next lower dose level once daily

Neutropenia

When Neutrophils	Recommended course[a]
Falls to <0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
For each subsequent drop below <0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

[a] at the physician's discretion, if neutropenia is the only toxicity at any dose level, add 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 ANC is 1.0 x 109 /l, and/or platelet counts are 50 x 10^9/L.

The recommended starting dose is lenalidomide 25 mg orally once daily days 1 to 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.

Dose reduction steps

	Lenalidomide[a]	Dexamethasone[a]
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[b]	Not applicable

[a] Dose reduction for all products can be managed independently

Thrombocytopenia

When platelets	Recommended course
Falls to <30 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a]
Returns 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> Day 15 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 falls to <0.5 x 10^9/L	Interrupt lenalidomide treatment
Returns to ≥1 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Returns 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
Returns to ≥0.5 x 10^9/L	Resume lenalidomide at next lower dose level once daily.

For a haematologic toxicity, the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no haematologic toxicity for at least 2 consecutive cycles: ANC ≥1.5 x 109 /L with a platelet count 100 x 10^9/L at the beginning of a new cycle).

1.1.3 Lenalidomide in combination with melphalan and prednisone followed by lenalidomide maintenance 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.

The recommended starting dose is lenalidomide 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 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 monotherapy as follows: 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression.

Dose reduction steps

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg[b]	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[c]	Not applicable	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 falls to <25 x 10^9/L Returns 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 falls to <0.5 x 10^9/L[a] Returns to ≥0.5 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns 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 Returns 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 lenalidomide if neutropenia was the only DLT. Otherwise, decrease by one dose level at start of next cycle.

1.2 Multiple Myeloma patients with at least one prior therapy

Lenalidomide treatment must not be started if the ANC <1.0 X 10^9/L, and/or platelet counts <75 X 10^9/L or, dependent on bone marrow infiltration by plasma cells, <30X10^9/L.

The recommended starting dose of lenalidomide is 25 mg orally once daily on Days I to 21 of repeated 28-day cycles. 1be recommended dose of dexamethasone is 40 mg orally once daily on Days I to 4, 9 to I2, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on Days 1 to 4 every 28 days. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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 Returns to ≥30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -1
For each subsequent drop below 30 x 10^9/L Returns to ≥30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily. Do not dose below 5 mg once daily.

Neutropenia

When Neutrophils	Recommended course
Falls to <0.5 x 10^9/L Returns to ≥0.5 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting 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 Returns 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.

1.3 Myelodysplastic Syndromes

Lenalidomide treatment must not be started if the 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 to 21 of repeated 28-day cycles.

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

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10 /L 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 anytime	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1, -2 or -3)

Neutropenia

When Neutropenia	Recommended course[a]
Fall to< 0.5 x 10 /1 Return to 0.5 x 10^9/1	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2 or -3)

Discontinuation of lenalidomide Recommended Course Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose Level-l, -2 or -3) 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 1 g/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
Falls to <50 x 10^9/L	Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days
Returns to ≥60 x 10^9/L	Resume lenalidomide at next lower dose 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
Returns to ≥60 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -2, -3, -4 or -5). Do not dose below dose level -5

Neutropenia

When Neutrophils	Recommended course[a]
Falls to <1.0 x 10^9/L for at least 7 days or Falls to <1.0 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
Returns to ≥1 x 10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop below 1.0 x 10^9/L for at least 7 days or drop to <1.0 x 10^9/L with associated fever (body temperature ≥38.5°C) or drop to <0.5 x 10^9/L Returns to ≥1.0 x 10^9/L	Interrupt lenalidomide treatment Resume Lenalidomide at next lower dose level (dose level -2, -3, -4, -5). Do not dose below dose level -5

2. Recommended dose adjustments for other toxicities.

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.

3. Venous and arterial thromboembolism

In patients with multiple myeloma, the combination of Lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone.

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with lenalidomide monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) than in patients with multiple myeloma treated with lenalidomide in combination therapy.

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) and was seen to a lesser extent with lenalidomide in combination with melphalan and prednisone. The risk of ATE is lower in patients with multiple myeloma treated with lenalidomide monotherapy than in patients with multiple myeloma treated with lenalidomide in combination therapy.

Action should be taken to try to minimise 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 primarily 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, 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)	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 1f patient 1s 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 to 21 of repeated 28-day cycles)
	Dose level-1*	2.5 mg once daily (Days 1 to 28 of repeated 28-day cycles)
	Dose level-2	2. 5 mg once every other day (Days 1 to 28 of repeated 28-day cycles)
Severe renal impairment (CLcr <30 mL/min, not requiring dialysis)	Starting dose	2. 5 mg once daily (Days 1 to 28 of repeated 28-day cycles)
	Dose level-1*	2.5 mg once every other day (Days 1 to 28 of repeated 28-day cycles)
	Dose level-2	2.5 mg twice a week (Days 1 to 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 to 28 of repeated 28-day cycles)
	Dose level-1*	2.5 mg every other day (Days 1 to 28 of repeated 28-day cycles)
	Dose level-2*	2.5 mg twice a week (Days 1 to 28 of repeated 28-day cycles)

*Recommended dose reduction steps during treatment and restart of treatment to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

4.3 Mantle cell lymphoma

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)	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 has commonly been observed in patients with chronic lymphocytic leukaemia (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.
Lenalidomide may be continued in patients with Grade 1 or 2 TFR without interruption or modification, at the physician's discretion. h1 patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to Grade 1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

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 haematologic 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 tumour 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 haematologic 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 tumour 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 lenalidomide 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 am1s 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 haematologic SPM must be taken into account before initiating treatment with Lenalidomide 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 mveloid 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 Lenalidomide in low- or intennediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-yeru· 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.

Consequently, the benefit/risk ratio of Lenalidomide 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 Lenalidomide 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 (I% cut-off level of strong nuclear staining, using immune-histochemical 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 dmg-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 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 is known to be a5sociated with liver dysfunction.

14. Disposal of unwanted medicine and other handling.

Capsules should not be opened or crushed. If powder from lenalidomide contacts the skin, the skin should be washed immediately and thoroughly with soap and water. if lenalidomide contacts the mucous membranes, they should be thoroughly flushed with water.

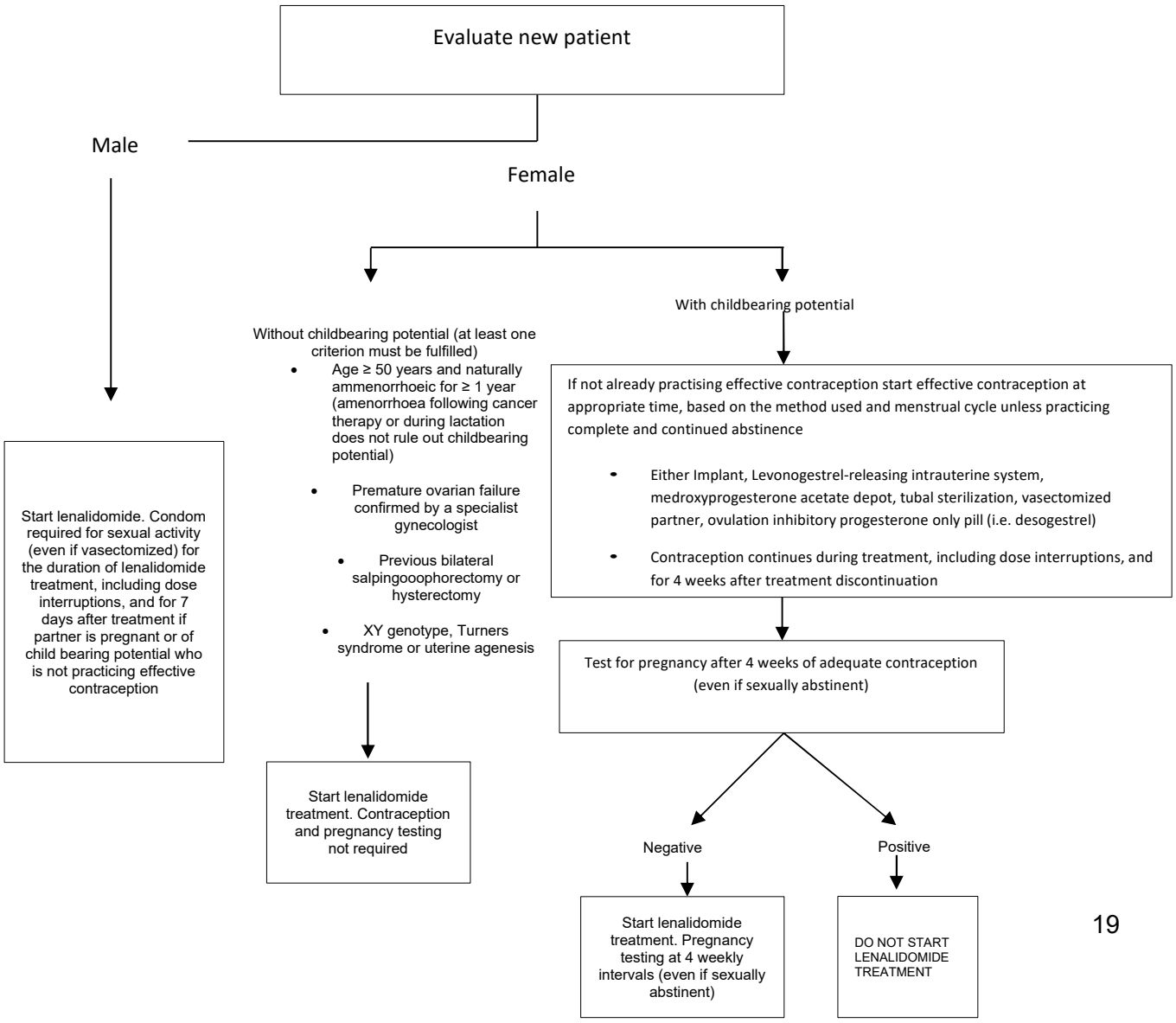
Patients should be advised never to give Lenalidomide to another person and to return any unused capsules to their pharmacist at the end of the treatment.

15. Blood donation

Patients should not donate blood during treatment and for 7 days after cessation of treatment with Lenalidomide. Local country specific arrangements for a prescription of Lenalidomide to be dispensed i.e. local description (local PPP requirements include dispensing to women of childbearing potential should occur within a maximum of 7 days from the prescription).

Pregnancy Prevention Programme

- Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance. Lenalidomide induced malformations in monkeys like those described for thalidomide. If Lenalidomide is taken in pregnancy, a teratogenic effect in humans is expected.
- Lenalidomide is therefore contraindicated in pregnancy. It is also contraindicated in women of childbearing potential unless all the conditions of the lenalidomide 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 or more (amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential).
  - ✓ Confirmed premature ovarian failure if confirmed by specialist gynaecologist.
  - ✓ Previous bilateral salpingo-oophorectomy, or hysterectomy
  - ✓ XY genotype, Turner syndrome, uterine agenesis.

  You are advised to refer your patient for a gynaecological opinion if you are unsure whether she meets these criteria.

- Prescriptions for women of child potential can be for a maximum duration of 4 consecutive weeks according to the approved indications dosing regimens (posology).

- Do not dispense to a woman of childbearing potential unless the pregnancy test is negative and was performed within three (3) days of the prescription.

- For those patients who are women of childbearing potential, prescriptions should be limited to a 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.

- For all other patients, prescriptions of lenalidomide should be limited to a maximum duration of 12 consecutive weeks and continuation of treatment requires a new prescription.

Safety Advice for Women of Childbearing Potential

- In view of the expected teratogenic risk of Lenalidomide Alvogen, 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 lenalidomide therapy, and even in case of dose interruption, or
  - ✓ commit to absolute and continuous sexual abstinence.
    AND
  - ✓ Have a medically supervised negative pregnancy test (with a minimum sensitivity of 25 mIU/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 continued sexual abstinence.

- Patients should be advised to inform the physician prescribing her contraception about the lenalidomide 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 in combination therapy, and to a lesser extent in patients with multiple myeloma 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 lenalidomide, she must stop treatment immediately and inform her physician immediately.

Safety Advice for Men

- In view of the expected teratogenic risk of lenalidomide, foetal exposure should be avoided.

- Lenalidomide 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 lenalidomide or shortly after he has stopped taking lenalidomide 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 if female patient
- ✓ Refer patient to a physician specialised or experienced in teratology for evaluation and advice.
  Pregnancy Capture Form is included in this pack
- ✓ Alvogen will wish to follow-up with you the progress of all pregnancies

Enclosures

- ✓ Checklists
- ✓ Pregnancy Reporting Form with local contact details
- ✓ Patient Card
- ✓ Patient brochure
- ✓ Local country specific details on the MDS PASS emphasizing that prior to prescribing Lenalidomide. the healthcare professionals should enroll the MDS patients into the PASS according to the national implementation of the MDS PASS as agreed on by the National Competent Authority (if applicable).

Reporting of Adverse Reactions

The safe use of lenalidomide is of paramount importance. As part of Alvogen's on-going safety monitoring, the company wishes to learn of Adverse Reactions that have occurred during the use of lenalidomide. Adverse Reaction report forms are included in this Health Care Professional Kit.

REPORTING OF ADVERSE REACTIONS

Suspected adverse reactions and medication errors should be reported either to:

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

Adalvo Limited

Malta Life Sciences Park,

Sir Temi Zammit,

Building 1, Level 4,

San Gwann Industrial Estate,

San Gwann, SGN 3000,

Malta

Email: pharmacovigilance@adalvo.com

Tel: +0040 727251514

Marketing Authorisation Holder

Adalvo Limited