Lenalidomide Te Arai

(lenalidomide)

Information for Healthcare Professionals - Brochure

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Introduction

Lenalidomide is an immunomodulating medicinal product.

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 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 therapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. The study showed a statistically significant prolongation of 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 PFS was 48.1 weeks in patients treated with lenalidomide/dexamethasone versus 20.0 weeks in patients treated with placebo/- dexamethasone. *

The efficacy and safety of lenalidomide has also been evaluated in low- or intermediate-1-risk MDS patients with a deletion-5q (q31-33) cytogenetic abnormality, with or without additional cytogenetic abnormalities. *

*text according to Data Sheet

- Lenalidomide Te Arai is indicated for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplantation.
- Lenalidomide Te Arai in combination with dexamethasone is indicated for the treatment of multiple myeloma patients whose disease has progressed after one therapy.

AND

- Lenalidomide Te Arai is indicated for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

- 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 4 mg/kg/day. Findings from this study showed that lenalidomide produced malformations (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 child bearing potential unless the conditions of the Lenalidomide Te Arai Restricted Access Programme described in this 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 must 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 cytopenias. 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. 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. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

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

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

Grade 3 or 4 thrombocytopenia was observed to a lesser extent in the Rd and Rd18 arms than in the comparator arm (8.1% vs 11.1%, respectively).

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

The combination of lenalidomide with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (34.1% in melphalan, prednisone and lenalidomide arm followed by lenalidomide [MPR+R] and melphalan, prednisone and lenalidomide followed by placebo [MPR+p] treated patients compared with 7.8% in MPp+p-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0 % in MPp+p treated patients;).

The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients).

Multiple myeloma with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasonetreated patients compared with 0.6% in placebo/dexamethasone-treated patients;). Grade 4 febrile neutropenia episodes were observed infrequently (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;).

Lenalidomide treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

For the indication described below:

• Dose is modified based upon clinical and laboratory findings.

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

Newly diagnosed multiple myeloma (NDMM)

• **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 count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 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	Not applicable

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

• *Thrombocytopenia*

When platelets	Recommended course
Fall to < 25 x 10^9/L Return to ≥ 50 x 10^9/L	Stop lenalidomide dosing for remainder of cycle[a] 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 Return to ≥ 1 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.

For hematologic 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 hematologic toxicity for at least 2 consecutive cycles: ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle).

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

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

Recommended dose

The recommended starting dose is lenalidomide 10 mg 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 5 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	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	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 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 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.

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

Multiple myeloma 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, platelet counts < 30 x 10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy 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 Return 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 Return 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
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment

Return to ≥0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose 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.

<u>Myelodysplastic Syndromes (MDS)</u>

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

Recommended dose

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

Dose Reduction Guidance

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

For patients who experience thrombocytopenia or neutropenia within the first 4 weeks of treatment:

Thrombocytopenia

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

Platelet count < 60 x 10^9/L	Fall by 50% of the baseline value Return to ≥ 30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg/day

Neutropenia

When baseline	When platelets	Recommended course
ANC ≥ 1 x 10^9/L	Fall to < 0.75 x 10^9/L Return to ≥ 1 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg/day
ANC < 1 x 10^9/L	Fall to < 0.5 x 10^9/L Return to ≥ 0.5 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg/day

For patients who experience thrombocytopenia after the first 4 weeks of treatment:

Thrombocytopenia

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

Neutropenia

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

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

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 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 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 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. 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.

Renal function (CLcr)	**Dose adjustment**	
	MM	**MDS**
Moderate renal impairment (30 ≤ CLcr< 50mL/min)	10 mg once daily[1]	5 mg once daily
Severe renal impairment (CLcr< 30 mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day	5 mg every other day
End Stage Renal Disease (ESRD) (CLcr <30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis.	5 mg, 3 times a week following each dialysis

[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. 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

8. 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.

9. 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) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

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

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the 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 tumor SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

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

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.

10. Infection with or without neutropenia

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

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

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

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

Reactivation of hepatitis B has been reported rarely in patients receiving lenalidomide who have previously been infected with 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.

11. 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.

12. Disposal of unwanted medicine and other handling

• Capsules should not be opened or crushed. Iodf powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with 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.

13. Blood donation

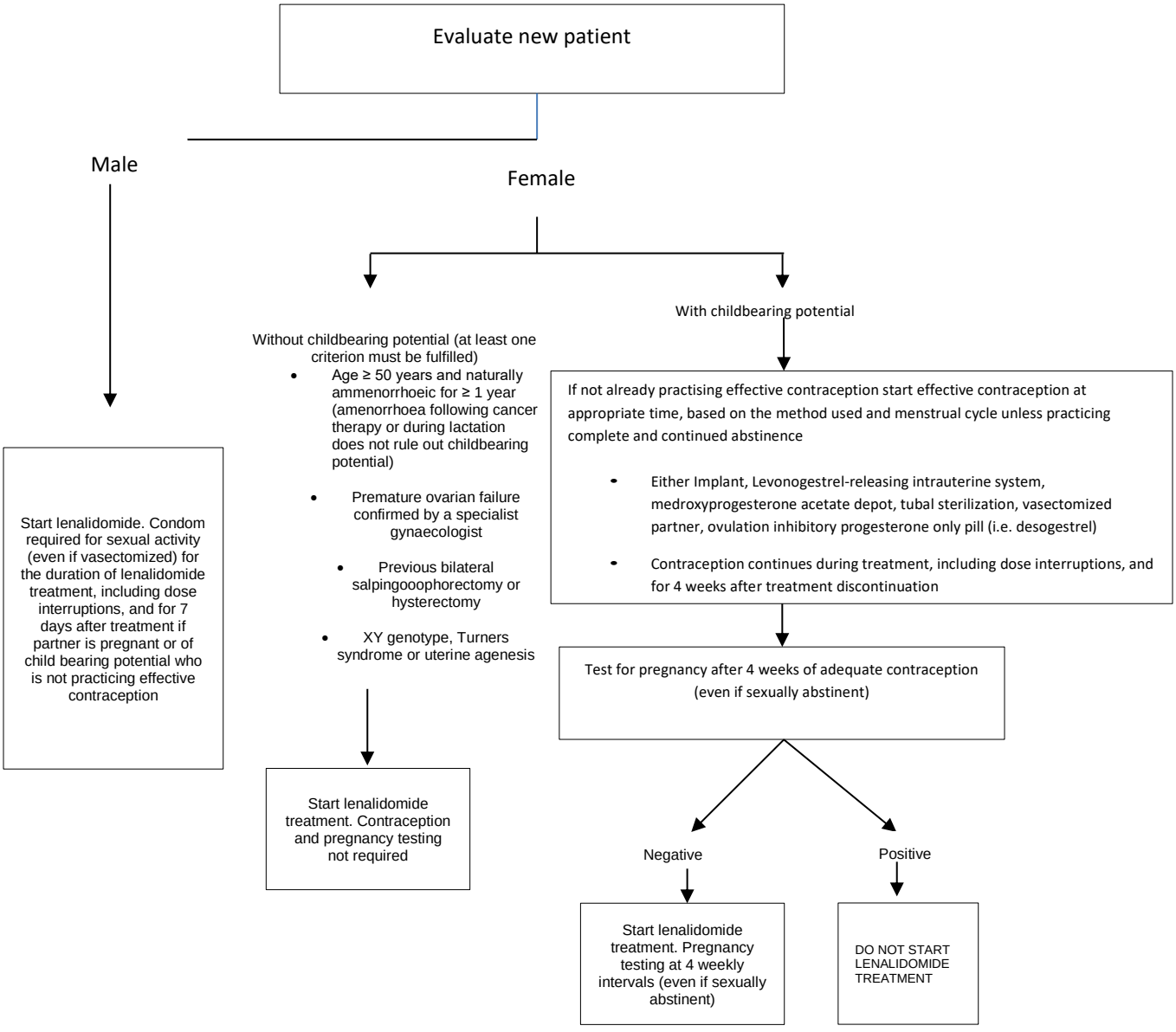
Patients should not donate blood during treatment and for 7 days after cessation of treatment with lenalidomide.

Lenalidomide Te Arai Restricted Access 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 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 Te Arai Restricted Access Programme are met.

• The Lenalidomide Te Arai Restricted Access 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 or not she meets these criteria.

Safety Advice for Women of Childbearing Potential

• In view of the expected teratogenic risk of lenalidomide, 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 child bearing 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. TI1e partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice

Lenalidomide Te Arai Restricted Access Programme Reporting

The requirements of the Lenalidomide Te Arai Restricted Access Programme are recorded online at www.lenalidomide.co.nz.

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.
- ✓ Notify Te Arai BioFarma of all such occurrences by using the Pregnancy Report Form found at www.lenalidomide.co.nz or by emailing lenalidomide@tearaibiofarma.com.
- ✓ Te Arai BioFarma will follow-up with you the progress of all pregnancies.

Reporting of Adverse Reactions

The safe use of lenalidomide is of paramount importance. As part of Te Arai BioFarma's ongoing safety monitoring, the company seeks 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 suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

Contact Details

For information and questions on the risk management of Te Arai BioFarma's products, and the Lenalidomide Te Arai Restricted Access Programme, please visit www.lenalidomide.co.nz or email lenalidomide@tearaibiofarma.com.