℞ **LENALIDOMIDE**

# LINADEX 5/10/15/20/25

5 mg/10 mg/15 mg/20 mg/25 mg Capsule

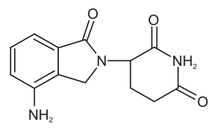
**Immunosuppressant**

**FORMULATION**

Lenalidomide Capsules 5 mg:
Each hard gelatin capsule contains: Lenalidomide.....5 mg
Lenalidomide Capsules 10 mg:
Each hard gelatin capsule contains: Lenalidomide.....10 mg
Lenalidomide Capsules 15 mg:
Each hard gelatin capsule contains: Lenalidomide.....15 mg
Lenalidomide Capsules 20 mg:
Each hard gelatin capsule contains: Lenalidomide.....20 mg
Lenalidomide Capsules 25 mg:
Each hard gelatin capsule contains: Lenalidomide.....25 mg

**DRUG DESCRIPTION**

**Lenalidomide Capsules 5 mg:**
White opaque cap and white opaque body, size '2' hard gelatin capsules imprinted with ' H' on cap and 'L2' on body, filled with off white to pale yellow color powder.
**Lenalidomide Capsules 10 mg:**
Orange opaque cap and white opaque body, size '0' hard gelatin capsules imprinted with ' H' on cap and 'L4' on body, filled with off white to pale yellow color powder.
**Lenalidomide Capsules 15 mg:**
Red opaque cap and white opaque body, size '0' hard gelatin capsules imprinted with ' H' on cap and 'L5' on body, filled with off white to pale yellow color powder.
**Lenalidomide Capsules 20 mg:**
Brown opaque cap and white opaque body, size '0' hard gelatin capsules imprinted with ' H' on cap and 'L6' on body, filled with off white to pale yellow color powder.
**Lenalidomide Capsules 25 mg:**
White opaque cap and white opaque body, size '0' hard gelatin capsules imprinted with ' H' on cap and 'L7' on body, filled with off white to pale yellow color powder.
Lenalidomide is described chemically as i.) 3-(4-Amino-1-oxo1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione ii.) 3-(4-Amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione iii.) 1-oxo-2(2,6-dioxopiperidine-3-yl)-4-aminoisoindoline. The molecular formula is $C_{13}H_{13}N_3O_3$ and the molecular weight is 259.27 The chemical structure of Lenalidomide is:



Lenalidomide is An off-white to pale-yellow powder ., and pKa acid value is found as less than 1.0. Slightly soluble in dimethyl formamide.
Lenalidomide Capsule contain the following inactive ingredients: Anhydrous Lactose (Supertab 21 AN), Microcrystalline Cellulose (Avicel PH 112), Croscarmellose sodium (Ac-Di-Sol), Magnesium stearate, Size '0' empty hard gelatin capsules with opaque orange cap and opaque white body, imprinted with 'H' on cap and 'L4' on body.

**THERAPEUTIC INDICATIONS**

**Multiple Myeloma**

Multiple myeloma
Lenalidomide as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
Lenalidomide as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.
Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.
Myelodysplastic syndromes
Lenalidomide as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia 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.
Mantle cell lymphoma
Lenalidomide as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

**POSOLOGY AND METHOD OF ADMINISTRATION**

Lenalidomide treatment should be supervised by a physician experienced in the use of anti-cancer therapies.
For all indications described below:

- Dose is modified based upon clinical and laboratory findings (see section 4.4).
- 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.
- In case of neutropenia, the use of growth factors in patient management should be considered.
- If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Posology
*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 ANC is $< 1.0 \times 10^9$/L, and/or platelet counts are $< 50 \times 10^9$/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] | Dexamethasonea |
|---|---|---|
| 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 all products can be managed independently

- *Thrombocytopenia*

| When platelets | Recommended course |
|---|---|
| Fall to $< 25 \times 10^9$/L | Stop lenalidomide dosing for remainder of cycle[a] |
| Return to $\geq 50 \times 10^9$/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.

- *NeutropeniaNeutropenia*

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

[c] 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.
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 $\geq 1{,}5 \times 10^9$/L with a platelet count $\geq 100 \times 10^9$/L at the beginning of a new cycle).

- Lenalidomide in combination with bortezomib and dexamethasone followed by lenalidomide and dexamethasone until disease progression in patients who are not eligible for transplant

*Initial treatment: Lenalidomide in combination with bortezomib and dexamethasone*
Lenalidomide in combination with bortezomib and dexamethasone must not be started if the ANC is $< 1.0 \times 10^9$/L, and/or platelet counts are $< 50 \times 10^9$/L.
The recommended starting dose is lenalidomide 25 mg orally once daily days 1-14 of each 21-day cycle in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m$^2$ body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day. For additional information on the dose, schedule and dose adjustments of medicinal products administered with lenalidomide, see Section 5.1 and the corresponding Summary of Product Characteristics.
Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended.
*Continued treatment: Lenalidomide in combination with dexamethasone until progression*
Continue lenalidomide 25 mg orally once daily on days 1-21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.

- *Dose reduction steps*

| | Lenalidomide[a] |
|---|---|
| Starting dose | 25 mg |
| Dose level -1 | 20 mg |
| Dose level -2 | 15 mg |
| Dose level -3 | 10 mg |
| Dose level- 4 | 5 mg |
| Dose level -5 | 2.5 mg |

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

- *Thrombocytopenia*

| When platelets | Recommended course |
|---|---|
| Fall to $< 30 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 50 \times 10^9$/L | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below 30 x $10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 50 \times 10^9$/L | Resume lenalidomide at next lower dose level once daily |

- *Neutropenia*

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

[c] 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.

- 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 $< 1.5 \times 10^9$/L, and/or platelet counts are $< 75 \times 10^9$/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 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*

| | Lenalidomid[a] | Melphalan | Prednisone |
|---|---|---|---|
| Starting dose | 10 mg* | 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 $< 25 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 25 \times 10^9$/L | Resume lenalidomide and melphalan at dose level -1 |
| For each subsequent drop below 30 x $10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 30 \times 10^9$/L | Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily. |

- *Neutropenia*

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

[c] 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.

- Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (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 $< 1.0 \times 10^9$/L, and/or platelet counts are $< 75 \times 10^9$/L.
*Recommended dose*
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) |
|---|---|---|
| | | |
| Dose level -2 | 5 mg (days 1-21 every 28 days) | 5 mg |
| Dose level -3 | Not applicable | 5 mg (days 1-21 every 28 days) |
| | Do not dose below 5 mg (days 1-21 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 $< 30 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 30 \times 10^9$/L | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below 30 x $10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 30 \times 10^9$/L | Resume lenalidomide at next lower dose level once daily |

- *Neutropenia*

| When neutrophils | Recommended coursea |
|---|---|
| Fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L | Resume lenalidomide at next lower dose level once daily. |

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.
*Multiple myeloma with at least one prior therapy*
Lenalidomide treatment must not be started if the ANC $< 1.0 \times 10^9$/L and/or platelet counts $< 75 \times 10^9$/L or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9$/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 $< 30 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 30 \times 10^9$/L | Resume lenalidomide at dose level -1 |
| For each subsequent drop below 30 x $10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 30 \times 10^9$/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 $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L when neutropenia is the only observed toxicity | Resume lenalidomide at starting dose once daily |
| Return to $\geq 0.5 \times 10^9$/L when dose-dependent haematological toxicities other than neutropenia are observed | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/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 |
|---|---|
| First fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/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.
*Mantle cell lymphoma (MCL)*
*Recommended dose*
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 days1 |
| [a] In countries where the 2.5 mg capsule is available. | 5 mg every other day on days 1 to 21, every 28 days |

- *Thrombocytopenia*

| When platelets | Recommended Course |
|---|---|
| Fall to $< 50 \times 10^9$/L | Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days |
| Return to $\geq 60 \times 10^9$/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 $\geq 60 \times 10^9$/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 |
|---|---|
| First fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L when neutropenia is the only observed toxicity | Resume lenalidomide at starting dose once daily |
| Return to $\geq 0.5 \times 10^9$/L when dose-dependent haematological toxicities other than neutropenia are observed | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L | Resume lenalidomide at next lower dose level once daily. |

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.
*Myelodysplastic syndromes (MDS)*
Lenalidomide treatment must not be started if the ANC $< 0.5 \times 10^9$/L and/or platelet counts $< 25 \times 10^9$/L.
*Recommended dose*
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

- *Dose reduction steps*

| | |
|---|---|
| Starting dose | 10 mg once daily on days 1 to 21 every 28 days |
| Dose level -1 | 5 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 1 to 28 every 28 days |

- *Thrombocytopenia*

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

- *Neutropenia*

| When neutrophils | Recommended course |
|---|---|
| Fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L | Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) |

*Discontinuation of lenalidomide*
Lenalidomide treatment must not be started if the ANC $< 0.5 \times 10^9$/L and/or platelet counts $< 25 \times 10^9$/L.
*Recommended dose*
The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 to 21 every 28 days.

- *Dose reduction steps*

| | |
|---|---|
| Starting dose | 10 mg once daily on days 1 to 21 every 28 days |
| Dose level -1 | 5 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 1 to 28 every 28 days |

- *Thrombocytopenia*

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

- *Neutropenia*

| When neutrophils | Recommended course |
|---|---|
| Fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/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.
*Mantle cell lymphoma (MCL)*
*Recommended dose*
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 days1 |
| [a] In countries where the 2.5 mg capsule is available. | 5 mg every other day on days 1 to 21, every 28 days |

- *Thrombocytopenia*

| When platelets | Recommended Course |
|---|---|
| Fall to $< 50 \times 10^9$/L | Interrupt lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days |
| Return to $\geq 60 \times 10^9$/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 $\geq 60 \times 10^9$/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 |
|---|---|
| First fall to $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L when neutropenia is the only observed toxicity | Resume lenalidomide at starting dose once daily |
| Return to $\geq 0.5 \times 10^9$/L when dose-dependent haematological toxicities other than neutropenia are observed | Resume lenalidomide at dose level -1 once daily |
| For each subsequent drop below $< 0.5 \times 10^9$/L | Interrupt lenalidomide treatment |
| Return to $\geq 0.5 \times 10^9$/L | Resume lenalidomide at next lower dose level once daily. |

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

- Lenalidomide maintenance in 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 1.6% 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 reduction may be required (see section 4.2).
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 (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with bortezomib and dexamethasone

Grade 4 neutropenia was observed at a lower frequency in the lenalidomide in combination with bortezomib and dexamethasone (RVd) arm compared to the Rd comparator arm (2.7% vs 5.9%) in the SWOG S0777 study. Grade 4 febrile neutropenia was reported at similar frequencies in the RVd arm and Rd arm (0.0% vs 0.4%). Patients should be advised to promptly report febrile episodes; a treatment interruption and/or dose reduction may be required (see section 4.2).
Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the RVd arm compared to the Rd comparator arm (17.2 % vs 9.4%).

- Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with low dose dexamethasone

Grade 4 neutropenia was observed in the lenalidomide arms in combination with 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, see section 4.8). 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, see section 4.8).
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: 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 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; see section 4.8).
The combination of lenalidomide with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (40.4% in MPR + R/MPR + p treated patients, compared with 13.7% in MPp + p-treated patients; see section 4.8).

- Multiple myeloma: patients 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/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8).
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; see section 4.8).

- Myelodysplastic syndromes

Lenalidomide treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (see section 4.8).

- Mantle cell lymphoma

Lenalidomide treatment in mantle cell lymphoma patients is associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm (see section 4.8).

*Thyroid disorders*
Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.
*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 lenalidomide in combination with dexamethasone or melphalan and prednisone or lenalidomide monotherapy or with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.
The combination of lenalidomide with intravenous bortezomib and dexamethasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. The frequency was lower when bortezomib was administered subcutaneously. For additional information, see Section 4.8 and the SmPC for bortezomib.
*Tumour flare reaction and tumour lysis syndrome*
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.
*Tumour burden*

- Mantle cell lymphoma

Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available.
*Early death*
In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, there were 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (40%) and 6/28 (21%) (See section 5.1).
*Adverse events*
In study MCL-002, during treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).
Patients with high tumour burden should therefore be closely monitored for adverse reactions (see Section 4.8) including signs of tumour flare reaction (TFR). Please refer to section 4.2 for dose adjustments for TFR.
High tumour burden was defined as at least one lesion $\geq 5$ cm in diameter or 3 lesions $\geq 3$ cm.
*Tumour flare reaction*

- Mantle cell lymphoma

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is $\geq 7$ cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (see section 4.2).
*Allergic reactions*
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). 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.
*Severe skin reactions*
Severe cutaneous reactions including SJS, and TEN and DRESS have been reported with the use of lenalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS 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.
*Lactose intolerance*
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
*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 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 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 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 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).
In newly diagnosed multiple myeloma patients receiving lenalidomide in combination with bortezomib and dexamethasone, the hematologic SPM incidence rate was 0.00 – 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 – 1.04 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 characterized, it should be kept in mind when considering and using Revlimid in this setting.
The incidence rate of hematologic 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 lenalidomide either in combination with melphalan or immedi

| | | |
|---|---|---|
| **Metabolism and Nutrition Disorders** | Very Common<br>Hypokalaemia◊,◊◊, Hyperglycaemia, Hypoglycaemia, Hypocalcaemia◊, Hyponatraemia◊, Dehydration◊◊, Decreased appetite◊◊, Weight decreased<br>Common<br>Hypomagnesaemia, Hyperuricaemia, Hypercalcaemia+ | Common<br>Hypokalaemia◊,◊◊, Hyperglycaemia, Hypocalcaemia◊, Diabetes mellitus◊, Hypophosphataemia, Hyponatraemia◊, Hyperuricaemia, Gout, Dehydration◊◊, Decreased appetite◊◊, Weight decreased |
| **Psychiatric Disorders** | Very Common<br>Depression, Insomnia<br>Uncommon<br>Loss of libido | Common<br>Depression, Insomnia |
| **Nervous System Disorders** | Very Common<br>Peripheral neuropathies◊◊, Paraesthesia, Dizziness◊◊, Tremor, Dysgeusia, Headache<br>Common<br>Ataxia, Balance impaired, Syncope◊◊, Neuralgia, Dysaesthesia | Very Common<br>Peripheral neuropathies◊◊<br>Common<br>Cerebrovascular accident◊, Dizziness◊◊, Syncope◊◊, Neuralgia<br>Uncommon<br>Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischemia |
| **Eye Disorders** | Very Common<br>Cataracts, Blurred vision<br>Common<br>Reduced visual acuity | Common<br>Cataract<br>Uncommon<br>Blindness |
| **Ear and Labyrinth Disorders** | Common<br>Deafness (Including Hypoacusis), Tinnitus | |
| **Cardiac Disorders** | Common<br>Atrial fibrillation◊,◊◊, Bradycardia<br>Uncommon<br>Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles | Common<br>Myocardial infarction (including acute)^,◊, Atrial fibrillation◊,◊◊, Congestive cardiac failure◊, Tachycardia, Cardiac failure◊,◊◊, Myocardial ischemia◊ |
| **Vascular Disorders** | Very Common<br>Venous thromboembolic events^, predominantly deep vein thrombosis and pulmonary embolism^,◊,◊◊, Hypotension◊◊<br>Common<br>Hypertension, Ecchymosis^ | Very Common<br>Venous thromboembolic events^, predominantly deep vein thrombosis and pulmonary embolism^,◊,◊◊<br>Common<br>Vasculitis, Hypotension◊◊, Hypertension<br>Uncommon<br>Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis |
| **Respiratory, Thoracic and Mediastinal Disorders** | Very Common<br>Dyspnoea◊,◊◊, Epistaxis^, Cough<br>Common<br>Dysphonia | Common<br>Respiratory distress◊, Dyspnoea◊,◊◊, Pleuritic pain◊◊, Hypoxia◊◊ |
| **Gastrointestinal Disorders** | Very Common<br>Diarrhoea◊,◊◊, Constipation◊, Abdominal pain◊◊, Nausea, Vomiting◊◊, Dyspepsia, Dry mouth, Stomatitis<br>Common<br>Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^,◊◊, Dysphagia<br>Uncommon<br>Colitis, Caecitis | Common<br>Gastrointestinal haemorrhage^,◊,◊◊, Small intestinal obstruction◊◊, Diarrhoea◊◊, Constipation◊, Abdominal pain◊◊, Nausea, Vomiting◊◊ |
| **Hepatobiliary Disorders** | Very Common<br>Alanine aminotransferase increased, Aspartate aminotransferase increased<br>Common<br>Hepatocellular injury◊◊, Abnormal liver function tests◊, Hyperbilirubinaemia<br>Uncommon<br>Hepatic failure^ | Common<br>Cholestasis◊, Hepatotoxicity, Hepatocellular injury◊◊, Alanine aminotransferase increased, Abnormal liver function tests◊<br>Uncommon<br>Hepatic failure^ |
| **Skin and Subcutaneous Tissue Disorders** | Very Common<br>Rashes◊◊, Pruritus<br>Common<br>Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema<br>Uncommon<br>Drug rash with eosinophilia and systemic symptoms◊◊, Skin discolouration, Photosensitivity reaction | Common<br>Rashes◊◊<br>Uncommon<br>Drug rash with eosinophilia and systemic symptoms◊◊ |
| **Musculoskeletal and Connective Tissue Disorders** | Very Common<br>Muscular weakness◊◊, Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊), Pain in extremity, Myalgia, Arthralgia◊<br>Common<br>Joint swelling | Common<br>Muscular weakness◊◊, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊)<br>Uncommon<br>Joint swelling |
| **Renal and Urinary Disorders** | Very Common<br>Renal failure (including acute)◊,◊◊<br>Common<br>Haematuria^, Urinary retention, Urinary incontinence<br>Uncommon<br>Acquired Fanconi syndrome | Uncommon<br>Renal tubular necrosis |
| **Reproductive System and Breast Disorders** | Common<br>Erectile dysfunction | |
| **General Disorders and Administration Site Conditions** | Very Common<br>Fatigue◊,◊◊, Oedema (including peripheral oedema), Pyrexia◊,◊◊, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors)<br>Common<br>Chest pain◊,◊◊, Lethargy | Very Common<br>Fatigue◊,◊◊<br>Common<br>Oedema peripheral, Pyrexia◊,◊◊, Asthenia |
| **Investigations** | Very Common<br>Blood alkaline phosphatase increased<br>Common<br>C-reactive protein increased | |
| **Injury, Poisoning and Procedural Complications** | Common<br>Fall, Contusion^ | |

◊◊ Adverse reactions reported as serious in clinical trials in patients with NDMM who had received lenalidomide in combination with bortezomib and dexamethasone

^See section 4.8 description of selected adverse reactions

◊Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone

+ Applies to serious adverse drug reactions only

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

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

*Tabulated summary from monotherapy*

The following tables are derived from data gathered during the main studies in monotherapy for myelodysplastic syndromes and mantle cell lymphoma.

**Table 3. ADRs reported in clinical trials in patients with myelodysplastic syndromes treated with lenalidomide#**

| System Organ Class / Preferred Term | All ADRs/Frequency | Grade 3-4 ADRs/Frequency |
|---|---|---|
| Infections and Infestations | Very Common<br>Bacterial, viral and fungal infections (including opportunistic infections)◊ | Very Common<br>Pneumonia◊<br>Common<br>Bacterial, viral and fungal infections (including opportunistic infections)◊, Bronchitis |
| Blood and Lymphatic System Disorders | Very Common<br>Thrombocytopenia^,◊, Neutropenia^,◊, Leucopenias | Very Common<br>Thrombocytopenia^,◊, Neutropenia^,◊, Leucopenias<br>Common<br>Febrile neutropenia^,◊ |
| Endocrine Disorders | Very Common<br>Hypothyroidism | |
| Metabolism and Nutrition Disorders | Very Common<br>Decreased appetite<br>Common<br>Iron overload, Weight decreased | Common<br>Hyperglycaemia◊, Decreased appetite |
| Psychiatric Disorders | | Common<br>Altered mood◊,~ |
| Nervous System Disorders | Very Common<br>Dizziness, Headache<br>Common<br>Paraesthesia | |
| Cardiac Disorders | | Common<br>Acute myocardial infarction^,◊, Atrial fibrillation◊, Cardiac failure◊ |
| Vascular Disorders | Common<br>Hypertension, Haematoma | Common<br>Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊ |
| Respiratory, Thoracic and Mediastinal Disorders | Very Common<br>Epistaxis^ | |
| Gastrointestinal Disorders | Very Common<br>Diarrhoea◊, Abdominal pain (including upper), Nausea, Vomiting, Constipation<br>Common<br>Dry mouth, Dyspepsia | Common<br>Diarrhoea◊, Nausea, Toothache |
| Hepatobiliary Disorders | Common<br>Abnormal liver function tests | Common<br>Abnormal liver function tests |
| Skin and Subcutaneous Tissue Disorders | Very Common<br>Rashes, Dry Skin, Pruritus | Common<br>Rashes, Pruritus |
| Musculoskeletal and Connective Tissue Disorders | Very Common<br>Muscle spasms, Musculoskeletal pain (including back pain◊ and pain in extremity), Arthralgia, Myalgia | Common<br>Back pain◊ |
| Renal and Urinary Disorders | | Common<br>Renal failure◊ |
| General Disorders and Administration Site Conditions | Very Common<br>Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache) | Common<br>Pyrexia |
| Injury, Poisoning and Procedural Complications | | Common<br>Fall |

^see section 4.8 description of selected adverse reactions

◊Adverse events reported as serious in myelodysplastic syndromes clinical trials

~ Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes phase 3 study; it was not reported as a grade 3 or 4 adverse event

Algorithm applied for inclusion in the SmPC: All ADRs captured by the phase 3 study algorithm are included in the EU SmPC. For these ADRs, an additional check of the frequency of the ADRs captured by the phase 2 study algorithm was undertaken and, if the frequency of the ADRs in the phase 2 study was higher than in the phase 3 study, the event was included in the EU SmPC at the frequency it occurred in the phase 2 study.

# Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase 3 study (double-blind safety population, difference between lenalidomide 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)

o All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo

o All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo

o All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo

- Myelodysplastic syndromes phase 2 study

o All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects

o All treatment-emergent grade 3 or 4 adverse|events in 1% of lenalidomide treated subjects

o All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects

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

| System Organ Class / Preferred Term | All ADRs/Frequency | Grade 3-4 ADRs/Frequency |
|---|---|---|
| Infections and Infestations | Very Common<br>Bacterial, viral and fungal infections (including opportunistic infections)◊, Nasopharyngitis, Pneumonia◊<br>Common<br>Sinusitis | Common<br>Bacterial, viral and fungal infections (including opportunistic infections)◊, Pneumonia◊ |
| Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps) | Common<br>Tumour flare reaction | Common<br>Tumour flare reaction, Squamous skin cancer^,◊ Basal cell carcinoma^,◊ |
| Blood and Lymphatic System Disorders | Very Common<br>Thrombocytopenia^, Neutropenia^,◊, Leucopenias◊, Anemia◊<br>Common<br>Febrile neutropenia^,◊ | Very Common<br>Thrombocytopenia^, Neutropenia^,◊, Anemia◊<br>Common<br>Febrile neutropenia^,◊, Leucopenias◊ |
| Metabolism and Nutrition Disorders | Very Common<br>Decreased appetite, Weight decreased, Hypokalaemia<br>Common<br>Dehydration◊ | Common<br>Dehydration◊, Hyponatraemia, Hypocalcaemia |
| Psychiatric Disorders | Common<br>Insomnia | |
| Nervous System Disorders | Common<br>Dysgeusia, Headache, neuropathy peripheral | Common<br>Peripheral sensory neuropathy, Lethargy |
| Ear and Labyrinth Disorders | Common<br>Vertigo | |
| Cardiac Disorders | | Common<br>Myocardial infarction (including acute)^,◊, Cardiac failure |
| Vascular Disorders | Common<br>Hypotension◊ | Common<br>Deep vein thrombosis◊, pulmonary embolism^,◊, Hypotension◊ |
| Respiratory, Thoracic and Mediastinal Disorders | Very Common<br>Dyspnoea◊ | Common<br>Dyspnoea◊ |
| Gastrointestinal Disorders | Very Common<br>Diarrhoea◊, Nausea◊, Vomiting◊, Constipation<br>Common<br>Abdominal pain◊ | Common<br>Diarrhoea◊, Abdominal pain◊, Constipation |
| Skin and Subcutaneous Tissue Disorders | Very Common<br>Rashes (including dermatitis allergic), Pruritus<br>Common<br>Night sweats, Dry skin | Common<br>Rashes |
| Musculoskeletal and Connective Tissue Disorders | Very Common<br>Muscle spasms, Back pain<br>Common<br>Arthralgia, Pain in extremity, Muscular weakness◊ | Common<br>Back pain, Muscular weakness◊, Arthralgia, Pain in extremity |
| Renal and Urinary Disorders | | Common<br>Renal failure◊ |
| General Disorders and Administration Site Conditions | Very Common<br>Fatigue, Asthenia◊, Peripheral oedema, Influenza like illness syndrome (including pyrexia◊, cough)<br>Common<br>Chills | Common<br>Pyrexia◊, Asthenia◊, Fatigue |

^see section 4.8 description of selected adverse reactions

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

- Mantle cell lymphoma controlled phase 2 study

o All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference in proportion between lenalidomide and control arm

o All treatment-emergent grade 3 or 4 adverse events in ≥ 1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm

o All Serious treatment-emergent adverse events in ≥ 1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm

- Mantle cell lymphoma single arm phase 2 study

o All treatment-emergent adverse events with ≥ 5% of subjects

o All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects

o All Serious treatment-emergent adverse events reported in 2 or more subjects

*Tabulated summary of post-marketing adverse reactions*

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

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

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

^see section 4.8 description of selected adverse reactions

Description of selected adverse reactions

*Teratogenicity*

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

*Neutropenia and thrombocytopenia*

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

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 4 neutropenia compared to placebo maintenance (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).

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 3 or 4 thrombocytopenia compared to placebo maintenance (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).

- Newly diagnosed multiple myeloma patients who are not eligible for transplant receiving lenalidomide in combination with bortezomib and dexamethasone

Grade 4 neutropenia was observed in the RVd arm to a lesser extent than in the Rd comparator arm (2.7% vs 5.9%) in the SWOG S0777 study. Grade 4 febrile neutropenia was reported at similar frequencies in the RVd arm compared to the Rd arm (0.0% vs 0.4%).

Grade 3 or 4 thrombocytopenia was observed in the RVd arm to a greater extent than in the Rd comparator arm (17.2 % vs 9.4%).

- Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with lenalidomide in combination with dexamethasone

The combination of lenalidomide with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 4 neutropenia (8.5% in Rd and Rd18, 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 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%).

- 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+R/MPR+p) compared with MPp+p (7.8%). 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 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

- Multiple myeloma: patients with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated 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).

- 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 3 study). Grade 3 or 4 febrile neutropenia episodes were observed in 2.2% of lenalidomide-treated patients compared with 0.0% in 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 3 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 2 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.

*Venous thromboembolism*

An increased risk of DVT and PE is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with lenalidomide in combination with melphalan and prednisone or in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma treated with lenalidomide monotherapy (see section 4.5).

Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

*Myocardial infarction*

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

*Haemorrhagic disorders*

Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

*Allergic reactions*

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

*Severe skin reactions*

Severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section 4.4).

*Second primary malignancies*

In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

*Acute myeloid leukaemia*

- Multiple myeloma

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following HDM/ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- Myelodysplastic syndromes

Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of lenalidomide in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

*Hepatic disorders*

The following post-marketing adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

*Rhabdomyolysis*

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

*Thyroid disorders*

Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

*Tumour flare reaction and tumour lysis syndrome*

In study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all report were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. There were no reports of TLS in study MCL-001 (see section 4.4).

*Gastrointestinal disorders*

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**OVERDOSE**

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

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

In MDS Del (5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of Del (5q) cells.

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

Clinical efficacy and safety

Lenalidomide efficacy and safety have been evaluated in six phase 3 studies in newly diagnosed multiple myeloma, two phase 3 studies in relapsed refractory multiple myeloma, one phase 3 study and one phase 2 study in myelodysplastic syndromes and one phase 2 study in mantle cell lymphoma as described below.

*Newly diagnosed multiple myeloma*

- Lenalidomide maintenance in patients who have undergone ASCT

The efficacy and safety of lenalidomide maintenance was assessed in two phase 3 multicenter, randomised, double-blind 2-arm, parallel group, placebo-controlled studies: CALGB 100104 and IFM 2005-02

*CALGB 100104*

Patients between 18 and 70 years of age with active MM requiring treatment and without prior progression after initial treatment were eligible.

Patients were randomised 1:1 within 90-100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on days 1-28 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 primary efficacy endpoint in the study was progression free survival (PFS) from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 460 patients were randomised: 231 patients to Lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

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

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 17 December 2009 (15.5 months follow up) showed a 62% reduction in risk of disease progression or death favoring lenalidomide (HR = 0.38; 95% CI 0.27, 0.54; p < 0.001). The median overall PFS was 33.9 months (95% CI NE, NE) in the lenalidomide arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm.

The PFS benefit was observed both in the subgroup of patients with CR and in the subgroup of patients who had not achieved a CR.

The results for the study, using a cut-off of 1 February 2016, are presented in Table 6

**Table 6 Summary of overall efficacy data**

| | Lenalidomide (N = 231) | Placebo (N = 229) |
|---|---|---|
| **Investigator-assessed PFS** | | |
| Median[a] PFS time, months (95% CI)[b] | **56.9** (41.9, 71.7) | **29.4** (20.7, 35.5) |
| HR [95% CI][c]; p-value[d] | **0.61** (0.48, 0.76); <0.001 | |
| **PFS2[e]** | | |
| Median[a] PFS2 time, months (95% CI)[b] | **80.2** (63.3, 101.8) | **52.8** (41.3, 64.0) |
| HR [95% CI]c ; p-value[d] | **0.61** (0.48, 0.78); <0.001 | |
| **Overall survival** | | |
| Median[a] OS time, months (95% CI)[b] | **111.0** (101.8, NE) | **84.2** (71.0, 102.7) |
| 8-year survival rate, % (SE) | 60.9 (3.78) | **44.6** (3.98) |
| HR [95% CI][c]; p-value[d] | **0.61** (0.46, 0.81); <0.001 | |
| **Follow-up** | | |
| Median[f] (min, max), months: all surviving patients | **81.9** (0.0, 119.8) | **81.0** (4.1, 119.5) |

CI = confidence interval; HR = hazard ratio; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival;

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

[b] The 95% CI about the median.

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

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

[e] Exploratory endpoint (PFS2). Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding was not considered as a second-line therapy.

[f] Median follow-up post-ASCT for all surviving subjects.

**Data cuts:** 17 Dec 2009 and 01 Feb 2016

*IFM 2005-02*

Patients aged < 65 years at diagnosis who had undergone ASCT and had achieved at least a stable disease response at the time of hematologic recovery were eligible. Patients were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on days 1-28 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 1-21 of a 28-day cycle). Treatment was to be continued until disease progression.

The primary endpoint was PFS defined from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 614 patients were randomised: 307 patients to lenalidomide and 307 patients to placebo.

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 SPMs (see Section 4.4).

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 7 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favoring lenalidomide (HR = 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 PFS benefit was less in the subgroup of patients with CR than in the subgroup of patients who had not achieved a CR.

The updated PFS, using a cut-off of 1 February 2016 (96.7 months follow up) continues to show a PFS advantage: HR = 0.57 (95% CI 0.47, 0.68; p < 0.001). The median overall PFS was 44.4 months (39.6, 52.0) in the lenalidomide arm versus 23.8 months (95% CI 21.2, 27.3) in the placebo arm. For PFS2, the observed HR was 0.80 (95% CI 0.66, 0.98; p = 0.026) for lenalidomide versus placebo. The median overall PFS2 was 69.9 months (95% CI 58.1, 80.0) in the lenalidomide arm versus 58.4 months (95% CI 51.1, 65.0) in the placebo arm. For OS, the observed HR was 0.90: (95% CI 0.72, 1.13; p = 0.355) for lenalidomide versus placebo. The median overall survival time was 105.9 months (95% CI 88.8, NE) in the lenalidomide arm versus 88.1 months (95% CI 80.7, 108.4) in the placebo arm.

- Lenalidomide in combination with bortezomib and dexamethasone in patients who are not eligible for stem cell transplantation

The SWOG S0777 study evaluated the addition of bortezomib to a foundation of lenalidomide and dexamethasone, as initial treatment, followed by continued Rd until disease progression, in patients with previously untreated multiple myeloma who are either ineligible for transplant or eligible for transplant with no plan to undertake immediate transplant.

Patients in the lenalidomide, bortezomib and dexamethasone (RVd) arm received lenalidomide 25 mg/day orally on days 1-14, intravenous bortezomib 1.3 mg/m² on days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of repeated 21-day cycles for up to eight 21-day cycles (24 weeks). Patients in the lenalidomide and dexamethasone (Rd) arm received lenalidomide 25 mg/day orally on days 1-21, and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles for up to six 21-day cycles (24 weeks). Patients in both arms took continued Rd: lenalidomide 25 mg/day orally on days 1-21 and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles. Treatment was to be continued until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 523 patients were enrolled into the study, with 263 patients randomised to RVd and 260 patients randomised to Rd. The demographics and disease-related baseline characteristics of the patients were well balanced between arms.

The results of PFS, as assessed by IRAC, at the time of the primary analysis, using a cut-off of 05 November 2015 (50.6 months follow up) showed a 24% reduction in risk of disease progression or death favoring RVd (HR = 0.76; 95% CI 0.61, 0.94; p = 0.010). The median overall PFS was 42.5 months (95% CI 34.0, 54.8) in the RVd arm versus 29.9 months (95% CI 25.6, 38.2) in the Rd arm. The benefit was observed regardless of eligibility for stem cell transplant.

The results for the study, using a cut-off of 01 December 2016, where the median follow-up time for all surviving subjects was 69.0 months, are presented in Table 9. The benefit favoring RVd was observed regardless of eligibility for stem cell transplant.

**Table 7. Summary of overall efficacy data**

| | Initial treatment | |
|---|---|---|
| | **RVd (3-week cycles × 8) (N = 263)** | **Rd (4-week cycles × 6) (N = 260)** |
| **IRAC-assessed PFS (months)** | | |
| Median[a] PFS time, months (95% CI)[b] | **41.7** (33.1, 51.5) | **29.7** (24.2, 37.8) |
| HR [95% CI][c]; p-value[d] | **0.76** (0.62, 0.94); 0.010 | |
| **Overall survival (months)** | | |
| Median[a] OS time, months (95% CI)[b] | **89.1** (76.1, NE) | **67.2** (58.4, 90.8) |
| HR [95% CI][c]; p-value[e] | **0.72** (0.56, 0.94); 0.013 | |
| **Response[f] – n (%)** | | |
| Overall response: CR, VGPR, or PR | 199 (75.7) | 170 (65.4) |
| ≥ VGPR | 153 (58.2) | 83 (31.9) |
| **Follow-up (months)** | | |
| Median[f] (min, max): all patients | 61.6 (0.2, 99.4) | 81.0 (4.1, 119.5) |

[a]CI = confidence interval; HR = hazard ratio; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival; Median follow-up was calculated from the date of randomization.

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

[c]Two-sided 95% CI about the median time.

[d]Based on unstratified Cox proportional hazards model comparing hazard functions associated with treatment arms (RVd:Rd).

[e]The p-value is based on unstratified log-rank test.

Data cutoff date = 01 Dec 2016.

Updated OS results, using a cut-off of 01 May 2018 (84.2 months median follow-up for surviving subjects) continue to show an OS advantage favoring RVd: HR = 0.73 (95% CI 0.57, 0.94; p=0.014). The proportion of subjects alive after 7 years was 54.7% in the RVd arm versus 44.7% in the Rd arm.

- Lenalidomide in combination with dexamethasone in patients who are not eligible for stem cell transplantation

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

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [CLcr] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 8:

**Table 8. Summary of overall efficacy data**

| | Rd (N = 535) | Rd18 (N = 541) | MPT (N = 547) |
|---|---|---|---|
| **Investigator-assessed PFS - (months)** | | | |
| Median[a] PFS time, months (95% CI)[b] | 26.0 (20.7, 29.7) | 21.0 (19.7, 22.4) | 21.9 (19.8, 23.9) |
| HR [95% CI][c]; p-valued | | | |
| Rd vs MPT | 0.69 (0.59, 0.80); <0.001 | | |
| Rd vs Rd18 | 0.71 (0.61, 0.83); <0.001 | | |
| Rd18 vs MPT | 0.99 (0.86, 1.14); 0.866 | | |
| **PFS2[e] - (months)** | | | |
| Median[a] PFS2 time, months (95% CI)[b] | 42.9 (38.1, 47.4) | 40.0 (36.2, 44.2) | 35.0 (30.4, 37.8) |
| HR [95% CI][c]; p-value[d] | | | |
| Rd vs MPT | 0.74 (0.63, 0.86); <0.001 | | |
| Rd vs Rd18 | 0.92 (0.78, 1.08); 0.316 | | |
| Rd18 vs MPT | 0.80 (0.69, 0.93); 0.004 | | |
| **Overall survival (months)** | | | |
| Median[a] OS time, months (95% CI)[b] | 58.9 (56.0, NE) | 56.7 (50.1, NE) | 48.5 (44.2, 52.0) |
| HR [95% CI][c]; p-value[d] | | | |
| Rd vs MPT | 0.75 (0.62, 0.90); 0.002 | | |
| Rd vs Rd18 | 0.91 (0.75, 1.09); 0.305 | | |
| Rd18 vs MPT | 0.83 (0.69, 0.99); 0.034 | | |
| Follow-up (months) | | | |
| Medianf (min, max): all patients | 40.8 (0.0, 65.9) | 40.1 (0.4, 65.7) | 38.7 (0.0, 64.2) |
| **Myeloma response[g] n (%)** | | | |
| CR | 81 (15.1) | 77 (14.2) | 51 (9.3) |
| VGPR | 152 (28.4) | 154 (28.5) | 103 (18.8) |
| PR | 169 (31.6) | 166 (30.7) | 187 (34.2) |
| Overall response: CR, VGPR, or PR | 402 (75.1) | 397 (73.4) | 341 (62.3) |
| **Duration of response - (months)[h]** | | | |
| Median[a] (95% CI)[b] | 35.0 (27.9, 43.4) | 22.1 (20.3, 24.0) | 22.3 (20.2, 24.9) |

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

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

[b]The 95% CI about the median.

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

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

[e]Exploratory endpoint (PFS2)

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

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

[h] data cut 24 May 2013

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

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

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

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

In an analysis of PFS, PFS2, OS using a cut-off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 9:

**Table 9. Summary of overall efficacy data**

| | MPR+R (N = 152) | MPR+p (N = 153) | MPp +p (N = 154) |
|---|---|---|---|
| **Investigator-assessed PFS - (months)** | | | |
| Median[a] PFS time, months (95% CI) | 27.4 (21.3, 35.0) | 14.3 (13.2, 15.7) | 13.1 (12.0, 14.8) |
| HR [95% CI]; p-value | | | |
| MPR+R vs MPp+p | 0.37 (0.27, 0.50); <0.001 | | |
| MPR+R vs MPR+p | 0.47 (0.35, 0.65); <0.001 | | |
| MPR+p vs MPp +p | 0.78 (0.60, 1.01); 0.059 | | |
| **PFS2 - (months) ^** | | | |
| Median[a] PFS2 time, months (95% CI) | 39.7 (29.2, 48.4) | 27.8 (23.1, 33.1) | 28.8 (24.3, 33.8) |
| HR [95% CI]; p-value | | | |
| MPR+R vs MPp+p | 0.70 (0.54, 0.92); 0.009 | | |
| MPR+R vs MPR+p | 0.77 (0.59, 1.02); 0.065 | | |
| MPR+p vs MPp +p | 0.92 (0.71, 1.19); 0.051 | | |
| **Overall survival (months)** | | | |
| Median[a] OS time, months (95% CI) | 55.9 (49.1, 67.5) | 51.9 (43.1, 60.6) | 53.9 (47.3, 64.2) |
| HR [95% CI]; p-value | | | |
| MPR+R vs MPp+p | 0.95 (0.70, 1.29); 0.736 | | |
| MPR+R vs MPR+p | 0.88 (0.65, 1.20); 0.43 | | |
| MPR+p vs MPp +p | 1.07 (0.79, 1.45); 0.67 | | |
| Follow-up (months) | | | |
| Median (min, max): all patients | 48.4 (0.8, 73.8) | 46.3 (0.5, 71.9) | 50.4 (0.5, 73.3) |
| **Investigator-assessed Myeloma response n (%)** | | | |
| CR | 30 (19.7) | 17 (11.1) | 9 (5.8) |
| PR | 90 (59.2) | 99 ( 64.7) | 75 (48.7) |
| Stable Disease (SD) | 24 (15.8) | 31 (20.3) | 63 (40.9) |
| Response Not Evaluable (NE) | 8 (5.3) | 4 (2.6) | 7 (4.5) |
| **Investigator-assessed Duration of response (CR+PR) - (months)** | | | |
| Median[a] (95% CI) | 26.5 (19.4, 35.8) | 12.4 (11.2, 13.9) | 12.0 (9.4, 14.5) |

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone; PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.

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

^PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomisation to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

*Supportive newly diagnosed multiple myeloma studies*

An open-label, randomised, multicenter, phase 3 study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomised to the lenalidomide/low dose dexamethasone arm, and 223 were randomised to the lenalidomide/standard dose dexamethasone arm. Patients randomised to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus dexamethasone 40 mg/day on days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomised to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

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

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

*Multiple myeloma with at least one prior therapy*

The efficacy and safety of lenalidomide were evaluated in two phase 3 multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone (len/dex) group took 25 mg of lenalidomide orally once daily on days 1 to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the len/dex group and 176 in the placebo/dex group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the len/dex group and 175 in the placebo/dex group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the len/dex and placebo/dex groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that len/dex was statistically significantly superior (p < 0.00001) to dexamethasone alone for the primary efficacy endpoint, TTP (median follow-up duration of 98.0 weeks). Complete response and overall response rates in the len/dex arm were also significantly higher than the placebo/dex arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dex group to receive treatment with the len/dex combination.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 10 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with len/dex (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dex (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with len/dex versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dex. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for len/dex and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dex. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the len/dex arm remain significantly higher than in the placebo/dex arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with len/dex versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dex. Despite the fact that 170 out of the 351 patients randomised to placebo/dex received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for len/dex relative to placebo/dex (HR = 0.833, 95% CI = [0.687, 1.009], p=0.045).

**Table 10. Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)**

| Endpoint | Len/dex (N=353) | Placebo/dex(N=351) | Placebo/dex(N=351) |
|---|---|---|---|
| **Time to event** | | | **HR [95% CI], p-value[a]** |
| Time to progression<br>Median [95% CI], weeks | 60.1 [44.3, 73.1] | 20.1 [17.7, 20.3] | 0.350 [0.287, 0.426], p < 0.001 |
| Progression free survival<br>Median [95% CI], weeks | 48.1<br>[36.4, 62.1] | 20.0 [16.1, 20.1] | 0.393 [0.326, 0.473], p < 0.001 |
| Overall survival<br>Median [95% CI], weeks<br>1-year Overall survival rate | 164.3 [145.1, 192.6]<br>82% | 136.4 [113.1, 161.7]<br>75% | 0.833 [0.687, 1.009], p = 0.045 |
| **Response rate** | | | **Odds ratio [95% CI], p-value[b]** |
| Overall response [n, %]<br>Complete response [n, %] | 212 (60.1)<br>58 (16.4) | 75 (21.4)<br>11 (3.1) | 5.53 [3.97, 7.71], p < 0.001<br>6.08 [3.13, 11.80], p < 0.001 |

[a] Two-tailed log rank test comparing survival curves between treatment groups.

[b] Two-tailed continuity-corrected chi-square test.

*Myelodysplastic syndromes*

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral lenalidomide (10 mg and 5 mg) versus placebo (MDS-004); and a phase 2, a multicentre, single-arm, open-label study of lenalidomide (10 mg) (MDS-003).

The results presented below represent the intent-to-treat population studied in MDS-003 and MDS-004; with the results in the isolated Del (5q) sub-population also shown separately.

In study MDS-004, in which 205 patients were equally randomised to receive lenalidomide 10 mg, 5 mg or placebo, the primary efficacy analysis consisted of a comparison of the transfusion-independence response rates of the 10 mg and 5 mg lenalidomide arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg lenalidomide and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg lenalidomide or continue lenalidomide treatment at higher dose (5 mg to 10 mg).

In, study MDS-003, in which 148 patients received lenalidomide at a dose of 10 mg, the primary efficacy analysis consisted of an evaluation of the efficacy of lenalidomide treatments to achieve haematopoietic improvement in subjects with low- or intermediate-1 risk myelodysplastic syndromes.

**Table 11. Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat populationEndpoint**

| | MDS-004 N = 205 | | | MDS-003 N = 148 |
|---|---|---|---|---|
| | 10 mg† N = 69 | 5 mg†† N = 69 | Placebo* N = 67 | 10 mg N = 148 |
| Transfusion Independence (≥ 182 days)# | 38 (55.1%) | 24 (34.8%) | 4 (6.0%) | 86 (58.1%) |
| Transfusion Independence (≥ 56 days)# | 42 (60.9%) | 33 (47.8%) | 5 (7.5%) | 97 (65.5%) |
| Median Time to Transfusion Independence (weeks) | 4.6 | 4.1 | 0.3 | 4.1 |
| Median Duration of Transfusion Independence (weeks) | NR∞ | NR | NR | 114.4 |
| Median Increase in Hgb, g/dL | 6.4 | 5.3 | 2.6 | 5.6 |

† Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles

† † Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles

* The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase

#Associated with an increase in Hgb of ≥ 1g/dL

∞ Not reached (i.e. the median was not reached)

In MDS-004, a significant larger proportion of patients with myelodysplastic syndromes achieved the primary endpoint of transfusion independence (>182 days) on lenalidomide 10 mg compared with placebo (55.1% vs. 6.0%). Amongst the 47 patients with an isolated Del (5q) cytogenetic abnormality and treated with lenalidomide 10 mg, 27 patients (57.4%) achieved red blood cell transfusion independence.

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.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of Health Related Quality of Life (HRQoL) and progression to acute myeloid leukaemia. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

In MDS-003, a large proportion of patients with myelodysplastic syndromes achieved transfusion independence (>182 days) on lenalidomide 10 mg (58.1%). The median time to transfusion independence was 4.1 weeks. The median duration of transfusion independence was 114.4 weeks. The median increase in haemoglobin (Hgb) was 5.6 g/dL. Major and minor cytogenetic responses were observed in 40.9% and 30.7% of subjects, respectively.

A large proportion of subjects enrolled in MDS-003 (72.9%) and MDS-004 (52.7%) had received prior erythropoiesis-stimulating agents.

*Mantle cell lymphoma*

The efficacy and safety of lenalidomide were evaluated in patients with mantle cell lymphoma in a phase 2, multicenter, randomised open-label study versus single agent of investigator's choice in patients who were refractory to their last regimen or had relapsed one to three times (study MCL-002).

Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomised 2:1 to the lenalidomide or the control arm. The investigator's choice treatment was selected before randomisation and consisted of monotherapy with either chlorambucil, cytarabine, rituximab, fludarabine, or gemcitabine.

Lenalidomide was administered orally 25 mg once daily for the first 21 days (D1 to D21) of repeating 28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.

The baseline demographic were comparable between the lenalidomide arm and control arm. Both patient populations presented a median age of 68.5 years with comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number of prior therapies.

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

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

**Table 12. Summary of efficacy results – study MCL-002, intent-to-treat population**

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

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

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

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

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

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

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

In study MCL-002 in the ITT population, there was an overall apparent increase in deaths within 20 weeks in the lenalidomide arm 22/170 (13%) versus 6/84 (7%) in the control arm. In patients with high tumour burden, corresponding figures were 16/81 (20%) and 2/28 (7%) (see section 4.4).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with lenalidomide in all subsets of the paediatric population in multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma (see section 4.2 for information on paediatric use).

**Pharmacokinetic properties**

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption

Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration ($C_{max}$) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in $C_{max}$ in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar among MM, MDS and MCL patients.

Distribution

*In vitro* ($^{14}$C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the medicinal product is undetectable in semen of a healthy subject 3 days after stopping the substance (see section 4.4).

Biotransformation and elimination

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with medicinal products that inhibit cytochrome P450 enzymes is not likely to result in metabolic medicinal product interactions in humans. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, lenalidomide is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

*In vitro* studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

*In vitro* studies indicate that lenalidomide has no inhibitory effect on human bile salt export pump (BSEP), BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2.

A majority of lenalidomide is eliminated through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 to 5 hours in patients with multiple myeloma, myelodysplastic syndromes or mantle cell lymphoma.

Older people

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence lenalidomide clearance (exposure in plasma). Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Renal impairment

The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total lenalidomide clearance decreases proportionally resulting in an increase in AUC. The AUC was increased by approximately 2.5, 4 and 5-fold in subjects with moderate renal impairment, severe renal impairment, and end-stage renal disease, respectively, compared to the group combining subjects with normal renal function and subjects with mild renal impairment. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of lenalidomide. The $C_{max}$ was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

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.

Other intrinsic factors

Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

**5.3 Preclinical safety data**

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

*In vitro* (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

**Availability**

**BLISTER PACK**: Alu - Alu blister pack x 10's (Box of 30's)

**STORAGE CONDITION**

Store at temperatures not exceeding 30°C.

**CAUTION**

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**ADR REPORTING STATEMENT:**

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction

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Date of First Authorization: 07/2022
Date of Revision of Package Insert: 07/2022

2069227