Lenzest 25

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5244544 LENZEST 25 CAPS

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Lenalidomide

Lenzest 25

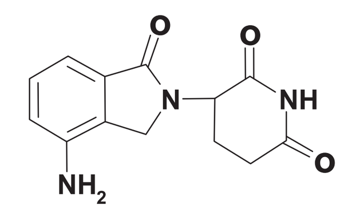
25 mg Capsule
Immunosuppressant

Formulation
Each capsule contains:
Lenalidomide....25 mg

Excipients: Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate.

Product Description
Hard gelatin capsules having white opaque cap and white opaque body imprinted with "RL" on cap and "83" on body with black ink containing white to off white granular powder.

Lenalidomide is a thalidomide analog with potential antineoplastic activity. Lenalidomide inhibits TNF-α production, stimulates T cells, reduces serum levels of the cytokines vascular endothelial growth factor and basic fibroblast growth factor, and inhibits angiogenesis.

Molecular Weight	259.26 g/mol
Molecular Formula	$^{C}13^{H}13^{N}3^{O}3$
IUPAC name	3-(7-amino-3-oxo-1H-isoindol-2-yl)piperidine-2,6-dione
Structural formula	

Pharmacodynamics and Pharmacokinetics[1]
Pharmacodynamic properties
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 withdeletions 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.

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 reported to be 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 studies 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 reported to be similar among MM, MDS and MCL patients.

Distribution
In vitro (^{14}C)-Lenalidomide binding to plasma proteins was reported to be 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 **Contraindication, Precaution, Warning**).

Biotransformation and elimination
Results from reported human *in vitro* metabolism studies indicated 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. Reported *in vitro* studies indicated 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.

Reported *in vitro* studies indicated 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.

Reported *in vitro* studies indicated 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 reported to be 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 reported 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 reported to be studied in subjects with renal impairment due to non-malignant 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 indicated 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 **Dosage and Mode/Route of Administration**.

Hepatic impairment
Reported population pharmacokinetic analyses included patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN or AST > ULN) and indicated that mild hepatic impairment does not influence Lenalidomide clearance (exposure in plasma). There are no reported data available for patients with moderate to severe hepatic impairment.

Other intrinsic factors
Reported 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.

Indications
Multiple myeloma
LENALIDOMIDE (Lenzest 25) 25 mg Capsule as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

LENALIDOMIDE (Lenzest 25) 25 mg Capsule as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section **Dosage and Mode/Route of Administration**) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

LENALIDOMIDE (Lenzest 25) 25 mg Capsule 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 (Lenzest 25) 25 mg Capsule 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 (Lenzest 25) 25 mg Capsule as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections **Contraindication, Precaution, Warning**).

Dosage and Administration
LENALIDOMIDE Capsules are available in the strengths of 10 mg and 25 mg and may not be suitable for all dosage recommendations given below. Therefore, other suitable available strengths and/or dosage forms of Lenalidomide should be used in such cases.

LENALIDOMIDE (Lenzest 25) 25 mg Capsule 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 **Contraindication, Precaution, Warning**).
- 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.

Dosage
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 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

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

The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue Lenalidomide and dexamethasone therapy until disease progression or intolerance.

- *Dose reduction steps*

	Lenalidomide[a]	Dexamethasone[a]
Starting dose	25 mg	40 mg
Dose level -1	20 mg	20 mg
Dose level -2	15 mg	12 mg
Dose level -3	10 mg	8 mg
Dose level- 4	5 mg	4 mg
Dose level -5	2.5 mg	Not applicable

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

- *Thrombocytopenia*

When platelets	Recommended course
Fall to < 25 x 10^9/L	Stop Lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/L	Decrease by one dose level when dosing resumed at next cycle

[a] If Dose limiting toxicity (DLT) occurs on > day 15 of a cycle, Lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

- *Neutropenia*

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

[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.

For hematologic toxicity the dose of Lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥ 1,5 x 10^9/L with a platelet count ≥ 100 x 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 x 10^9/L, and/or platelet counts are < 50 x 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 corresponding Package insert for bortezomib and dexamethasone.

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 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 50 x 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 ≥ 50 x 10^9/L	Resume Lenalidomide at next lower dose level once daily

- *Neutropenia*

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

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

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

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*

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg	0.14 mg/kg	1 mg/kg
Dose level -2	5 mg	0.10 mg/kg	0.5 mg/kg
Dose level -3	2.5 mg	Not applicable	0.25 mg/kg

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

- *Thrombocytopenia*

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

- *Neutropenia*

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

[a]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 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

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

- *Dose reduction steps*

	Starting dose (10 mg)	If dose increased (15 mg)[a]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (days 1-21 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 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 30 x 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 ≥ 30 x 10^9/L	Resume Lenalidomide at next lower dose level once daily

- *Neutropenia*

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

[a]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 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

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

- *Dose reduction steps*

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

- *Thrombocytopenia*

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

- *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume Lenalidomide at starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume Lenalidomide at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume Lenalidomide at next lower dose level (dose level - 1, -2 or -3) once daily. Do not dose below 5 mg 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 x 10^9/L and/or platelet counts < 25 x 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 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 25 x 10^9/L - < 50 x 10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/L at any time	Resume Lenalidomide at next lower dose level (dose level - 1, -2 or -3)

- *Neutropenia*

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

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

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 days[1] 5 mg every other day on days 1 to 21, every 28 days

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

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 50 x 10^9/L	Interrupt Lenalidomide treatment and conduct Complete Blood Count (CBC) at least every 7 days
Return to ≥ 60 x 10^9/L	Resume Lenalidomide at next lower level (dose level - 1)
For each subsequent drop below 50 x 10^9/L Return to ≥60 x 10^9/L	Interrupt Lenalidomide treatment and conduct the CBC at least every 7 days Resume Lenalidomide at next lower level (dose level -2, -3, -4 or -5). Do not dose below dose level -5

- *Neutropenia*

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

Tumour flare reaction
Lenalidomide may be continued in patients with Grade 1 or 2 tumour flare reaction (TFR) without interruption or modification, at the physician's discretion. In patients with Grade 3 or 4 TFR, withhold treatment with Lenalidomide until TFR resolves to ≤ Grade 1 and patients may be treatedfor management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section **Contraindication, Precaution, Warning**).

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

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

Special populations
- *Paediatric population*

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

- *Elderly*

Currently available pharmacokinetic data are described in section **Pharmacodynamics and Pharmacokinetics, Pharmacokinetic properties**. Lenalidomide has been used in clinical studies in multiple myeloma patients up to 91 years of age, in myelodysplastic syndromes patients up to 95 years of age and in mantle cell lymphoma patients up to 88 years of age.

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.

Newly diagnosed multiple myeloma: patients who are not eligible for transplant
Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section **Contraindication, Precaution, Warning**).

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

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

In patients with newly diagnosed multiple myeloma aged 75 years and older who received Lenalidomide, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation.

Lenalidomide combined therapy was less tolerated in newly diagnosed multiple myeloma patients older than 75 years of age compared to the younger population. These patients discontinued at a higher rate due to intolerance (Grade 3 or 4 adverse events and serious adverse events), when compared to patients < 75 years.

Multiple myeloma: patients with at least one prior therapy
The percentage of multiple myeloma patients aged 65 or over was not significantly different between the Lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was reported between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out.

Myelodysplastic syndromes
For myelodysplastic syndromes patients treated with Lenalidomide, no overall difference in safety and efficacy was reported between patients aged over 65 and younger patients.

Mantle cell lymphoma
For mantle cell lymphoma patients treated with Lenalidomide, no overall difference in safety and efficacy was reported between patients aged 65 years or over compared with patients aged under 65 years of age.

- *Patients with renal impairment*

Lenalidomide is primarily excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section **Contraindication, Precaution, Warning**). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma, myelodysplastic syndromes or mantle cell lymphoma.

The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.

There are no phase 3 study reported with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

Multiple myeloma

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

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

Myelodysplastic syndromes

Renal function (CLcr)	Dose adjustment	
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	Starting dose	5 mg once daily (days 1 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg once daily (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg once every other day (days 1 to 28 of repeated 28-day cycles)
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1 to 28 of repeated 28-day cycles)
End Stage Renal Disease (ESRD) (Clcr < 30 mL/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1 to 21 of repeated 28-day cycles)
	Dose level -1*	2.5 mg every other day (days 1 to 28 of repeated 28-day cycles)
	Dose level -2*	2.5 mg twice a week (days 1 to 28 of repeated 28-day cycles)

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

Mantle cell lymphoma

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

[1]The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.
[2]In countries where the 7.5 mg capsule is available.
After initiation of Lenalidomide therapy, subsequent Lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

- *Patients with hepatic impairment*

Lenalidomide has not been reported to be studied in patients with impaired hepatic function and there are no specific dose recommendations.

Method of administration
Oral use.

LENALIDOMIDE (Lenzest 25) 25 mg Capsule should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

- **Contraindications, Precautions, Warnings**

Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section **Formulation/ composition**
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections **Contraindications, Precautions, Warnings** and **Pregnancy and Lactation**)

Warnings and Precautions
When Lenalidomide is given in combination with other medicinal products, the corresponding Package insert must be consulted prior to initiation of treatment.

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

Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:
- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Counselling
For women of childbearing potential, Lenalidomide is contraindicated unless all of the following are met:
- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as Lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of Lenalidomide.

For male patients taking Lenalidomide, pharmacokinetic data has reported that Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section **Pharmacodynamics and Pharmacokinetics, Pharmacokinetic properties**). As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking Lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for at least 7 days after dose interruptions and/or cessation of treatment
- Understand that if his female partner becomes pregnant whilst he is taking Lenalidomide or shortly after he has stopped taking Lenalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception
Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after Lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:
- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking Lenalidomide in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking Lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see also section **Interactions**). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section **Interactions**).Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

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

Pregnancy testing
Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of Lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when Lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with Lenalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment for safe disposal.

Patients should not donate blood during therapy or for at least 7 days following discontinuation of Lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to Lenalidomide, the marketing authorisation holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of Lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of Lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks, and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks.

Other special warnings and precautions for use
Myocardial infarction
Myocardial infarction has been reported in patients receiving Lenalidomide, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

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

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

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

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis– should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving Lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

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

Neutropenia and thrombocytopenia
The major dose limiting toxicities of Lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of Lenalidomide treatment and monthly thereafter to monitor for cytopenias. In mantle cell lymphoma patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then at the start of each cycle. A dose reduction may be required (see section **Dosage and Mode/Route of Administration**).

In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes.

Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section **Adverse drug reactions**, Haemorrhagic disorders).

Co-administration of Lenalidomide with other myelosuppressive agents should be undertaken with caution.

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

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

Overall, grade 4 neutropenia was reported at a higher frequency in the Lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating Lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in reported study and 16.4% vs 0.7% in reported study, respectively). Treatment-emergent AEs of neutropenia leading to Lenalidomide discontinuation were reported in 2.2% of patients in reported study and 2.4% of patients in reported study, 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 reported study and 0.3% vs 0% in reported study, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reduction may be required (see section **Dosage and Mode/Route of Administration**).

Grade 3 or 4 thrombocytopenia was reported at a higher frequency in the Lenalidomide maintenance arms compared to the placebo maintenance arms in reported 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 reported study and 13.0% vs 2.9% in reported study, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receivingconcomitant medicinal products susceptible to induce bleeding (see section **Adverse drug reactions**, 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 reported 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 reported 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 **Dosage and Mode/Route of Administration**).

Grade 3 or 4 thrombocytopenia was reported 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 reported 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 **Adverse drug reactions**). 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 **Adverse drug reactions**).

Grade 3 or 4 thrombocytopenia was reported 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 reported clinical studies 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 **Adverse drug reactions**). Grade 4 febrile neutropenia episodes were reported infrequently (1.7% in MPR+R/MPR+p treated patients compared to 0.0% in MPp+p treated patients; see section **Adverse drug reactions**).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 **Adverse drug reactions**).

- *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 **Adverse drug reactions**). Grade 4 febrile neutropenia episodes were reported infrequently (0.6% in Lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section **Adverse drug reactions**).

The combination of Lenalidomide with dexamethasone in multiple myeloma patients is reported to be 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 **Adverse drug reactions**).

- *Myelodysplastic syndromes*

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

- *Mantle cell lymphoma*

Lenalidomide treatment in mantle cell lymphoma patients is reported to be associated with a higher incidence of grade 3 and 4 neutropenia compared with patients on the control arm (see section **Adverse drug reactions**).

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 reported 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 **Adverse drug reactions** and the Package insert 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 reported 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 reported study there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumor burden at baseline are at increased risk of early death, there were 20% early deaths reported in the Lenalidomide arm and 7% early deaths reported in the control arm. Within 52 weeks corresponding figures were 40% and 21%.

Adverse events
In reported study, during treatment cycle 1, 14% patients with high tumour burden were withdrawn from therapy in the Lenalidomide arm vs. 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, 64%.

Patients with high tumour burden should therefore be closely monitored for adverse reactions (see section **Adverse drug reactions**) including signs of tumour flare reaction (TFR). Please refer to section **Dosage and Mode/Route of Administration** for dose adjustments for TFR.

High tumour burden was defined as at least one lesion ≥ 5 cm in diameter or 3 lesions ≥ 3 cm.

Tumour flare reaction
- *Mantle cell lymphoma*

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in reported studies experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of

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TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (see section **Dosage and Mode/Route of Administration**).

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with Lenalidomide (see section **Adverse drug reactions**). 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 skinreaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive Lenalidomide.

Second primary malignancies
An increase of second primary malignancies (SPM) has been reported in clinical studies 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 reported clinical studies 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 reported 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 reported 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 reported to be 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 reported 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 reported to be 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 Lenalidomide 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 immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS
- *Karyotype*

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

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

- *TP53 status*

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

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

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with Lenalidomide in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug- induced hepatotoxicity remain unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

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

Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections was reported with Lenalidomide in combination with dexamethasone than with MPT in patients with NDMM who are not eligible for transplant, and with Lenalidomide maintenance compared to placebo in patients with NDMM who had undergone ASCT. Grade ≥ 3 infections reported within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

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

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

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

Progressive multifocal leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with Lenalidomide. PML was reported several months to several years after starting the treatment with Lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, Lenalidomide must be permanently discontinued.

Newly diagnosed multiple myeloma patients
A higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) was reported in patients with age > 75 years, ISS stage III, ECOG PS≥2 or CLcr<60 mL/min when Lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate Lenalidomide in combination, with consideration to age, ISS stage III, ECOG PS≥2 or CLcr<60 mL/min (see sections **Dosage and Mode/Route of Administration** and **Adverse drug reactions**).

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

Effects on ability to drive and use machines
Lenalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of Lenalidomide. Therefore, caution is recommended when driving or operating machines.

Excipients warnings
This medicine contains lactose, therefore patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, or glucose-galactose malabsorption should not take this medicine.

- **Pregnancy and Lactation**[1]

Due to the teratogenic potential, Lenalidomide must be prescribed under a Pregnancy Prevention Programme (see section **Contraindications, Precautions, Warnings**) unless there is reliable evidence that the patient does not have childbearing potential.

Pregnancy
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. Therefore, a teratogenic effect of Lenalidomide is expected and Lenalidomide is contraindicated during pregnancy (see section **Contraindications, Precautions, Warnings**).

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with Lenalidomide, treatment must be stopped and the patient shouldbe referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking Lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section **Pharmacodynamics and Pharmacokinetics, Pharmacokinetic properties**). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking Lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Fertility
A reported fertility study in rats with Lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

Lactation
It is not known whether Lenalidomide is excreted in breast milk. Therefore breast-feeding should be discontinued during therapy with Lenalidomide.

Interactions[1]
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving Lenalidomide with dexamethasone (see sections Contraindications, Precautions, Warnings and Adverse drug reactions).

Oral contraceptives
No interaction study has been reported with oral contraceptives. Lenalidomide is not an enzyme inducer. In an reported *in vitro* study with human hepatocytes, Lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if Lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may bereduced during treatment. Effective measures to avoid pregnancy must be taken (see sections **Contraindications, Precautions, Warnings** and **Pregnancy and Lactation**).

Warfarin
Co-administration of multiple 10 mg doses of Lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of Lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin
Concomitant administration with Lenalidomide 10 mg once daily reported to increase the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%- 28.2%]. It is not known whether the effect will be different in the clinical use (higher Lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during Lenalidomide treatment.

Statins
There is an increased risk of rhabdomyolysis when statins are administered with Lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

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

Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, Lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of Lenalidomide (25 mg). Co-administration of Lenalidomide does not alter the pharmacokinetics of temsirolimus.

- **Adverse drug reactions**[1]

Summary of the safety profile
Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with Lenalidomide maintenance
A conservative approach was applied to determine the adverse reactions from reported study. The adverse reactions described in Table 1 included events reported post-HDM/ASCT as well as events from the maintenance treatment period. A second analysis that identified events that reported after the start of maintenance treatment suggests that the frequencies described in Table 1 may be higher than actually reported during the maintenance treatment period. In reported study, the adverse reactions were from the maintenance treatment period only.

The serious adverse reactions reported more frequently (≥5%) with Lenalidomide maintenance than placebo were:
- Pneumonias (10.6%; combined term)
- Lung infection (9.4% [9.4% after the start of maintenance treatment])

In the reported study, the adverse reactions observed more frequently with Lenalidomide maintenance than placebo were neutropenia (60.8%), bronchitis (47.4%), diarrhoea (38.9%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), asthenia (29.7%), cough (27.3%), thrombocytopenia (23.5%), gastroenteritis (22.5%) and pyrexia (20.5%).

In the reported study, the adverse reactions reported more frequently with Lenalidomide maintenance than placebo were neutropenia (79.0% [71.9% after the start of maintenance treatment]), thrombocytopenia (72.3% [61.6%]), diarrhoea (54.5% [46.4%]), rash (31.7% [25.0%]), upper respiratory tract infection (26.8% [26.8%]), fatigue (22.8% [17.9%]), leucopenia (22.8% [18.8%]) and anemia (21.0% [13.8%]).

Newly diagnosed multiple myeloma patients who are not eligible for transplant receiving Lenalidomide in combination with bortezomib and dexamethasone
In the reported study, the serious adverse reactions reported more frequently (≥ 5%) with Lenalidomide in combination with intravenous bortezomib and dexamethasone than with Lenalidomide in combination with dexamethasone were:
- Hypotension (6.5%), lung infection (5.7%), dehydration (5.0%)

The adverse reactions reported more frequently with Lenalidomide in combination with bortezomib and dexamethasone than with Lenalidomide in combination with dexamethasone were: Fatigue (73.7%), peripheral neuropathy (71.8%), thrombocytopenia (57.6%), constipation (56.1%), hypocalcaemia (50.0%).

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with Lenalidomide in combination with low dose dexamethasone
The serious adverse reactions reported more frequently (≥5%) with Lenalidomide in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:
- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

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

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with Lenalidomide in combination withmelphalan and prednisone
The serious adverse reactions reported more frequently (≥5%) with melphalan, prednisone and Lenalidomide followed by Lenalidomide maintenance (MPR+R) or melphalan, prednisone and Lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:
- Febrile neutropenia (6.0%)
- Anemia (5.3%)

The adverse reactions reported more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Multiple myeloma: patients with at least one prior therapy
In reported two phase 3 placebo-controlled studies, patients with multiple myeloma were exposed to the Lenalidomide/dexamethasone combination and to the placebo/dexamethasone combination.The most serious adverse reactions reported more frequently in Lenalidomide/dexamethasone than placebo/dexamethasone combination were:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section **Contraindication, Precaution, Warning**)
- Grade 4 neutropenia (see section **Contraindication, Precaution, Warning**).

The reported adverse reactions which occurred more frequently with Lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical studies were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Myelodysplastic syndromes
The overall safety profile of Lenalidomide in patients with myelodysplastic syndromes is based on reported data from patients from one phase 2 study and one phase 3 study. In the phase 2, all patients were on Lenalidomide treatment. In the phase 3 study, patients were on Lenalidomide 5 mg, 10 mg and on placebo during the double-blind phase of the study.

Most adverse reactions tended to occur during the first 16 weeks of therapy with Lenalidomide. Serious adverse reactions include:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section **Contraindications, Precautions, Warnings**)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section **Contraindications, Precautions, Warnings**).

The most commonly observed adverse reactions which occurred more frequently in the Lenalidomide groups compared to the control arm in the phase 3 study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Mantle cell lymphoma
The overall safety profile of Lenalidomide in patients with mantle cell lymphoma is based on reported data from patients from a phase 2 randomised, controlled study.

Additionally, adverse drug reactions from supportive study have been included in table 3.

The serious adverse reactions reported more frequently in study (with a difference of at least 2 percentage points) in the Lenalidomide arm compared with the control arm were:
- Neutropenia (3.6%)
- Pulmonary embolism (3.6%)
- Diarrhoea (3.6%)

The most frequently reported adverse reactions which occurred more frequently in the Lenalidomide arm compared with the control arm in study were neutropenia (50.9%), anemia (28.7%), diarrhoea (22.8%), fatigue (21.0%), constipation (17.4%), pyrexia (16.8%), and rash (including dermatitis allergic) (16.2%).

In study reported 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, 20% early deaths in the Lenalidomide arm and 7% early deaths in the control arm. Within 52 weeks corresponding figures were 39.5% and 21%.

During treatment cycle 1, 14% patients with high tumour burden were withdrawn from therapy in the Lenalidomide arm vs. 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, 64%.

High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

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

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

Tabulated summary for monotherapy in MM
The following table is derived from data gathered during reported NDMM studies in patients who have undergone ASCT treated with Lenalidomide maintenance. The reported data were not adjusted according to the longer duration of treatment in the Lenalidomide-containing arms continued until disease progression versus the placebo arms in the pivotal multiple myeloma studies.

Table 1. ADRs reported in clinical studies in patients with multiple myeloma treated with Lenalidomide maintenance therapy

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonias[◊,a], Upper respiratory tract infection, Neutropenic infection, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Sinusitis, Nasopharyngitis, Rhinitis Common Infection[◊], Urinary tract infection[◊,*], Lower respiratory tract infection, Lung infection[◊]	Very Common Pneumonias[◊,a], Neutropenic infection Common Sepsis[◊,b], Bacteraemia, Lung infection[◊], Lower respiratory tract infection bacterial, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Herpes zoster[◊], Infection[◊]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome[◊,*]	
Blood and Lymphatic System Disorders	Very Common Neutropenia ^,◊, Febrile neutropenia ^,◊, Thrombocytopenia ^,◊, Anemia, Leucopenia[◊], Lymphopenia	Very Common Neutropenia ^,◊, Febrile neutropenia ^,◊, Thrombocytopenia ^,◊, Anemia, Leucopenia[◊], Lymphopenia Common Pancytopenia[◊]
Metabolism and Nutrition Disorders	Very Common Hypokalaemia	Common Hypokalaemia, Dehydration
Nervous System Disorders	Very Common Paraesthesia Common Peripheral neuropathy[c]	Common Headache
Vascular Disorders	Common Pulmonary embolism[◊,*]	Common Deep vein thrombosis ^,◊,d
Respiratory, Thoracic and Mediastinal Disorders	Very Common Cough Common Dyspnoea[◊], Rhinorrhoea	Common Dyspnoea[◊]
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash, Dry skin	Common Rash, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms Common Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue, Asthenia

◊ Adverse reactions reported as serious in clinical studies in patients with NDMM who had undergone ASCT
* Applies to serious adverse drug reactions only
^ See section **Adverse drug reactions** description of selected adverse reactions
a "Pneumonias" combined AE term includes the following PTs: Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis
b "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis
c "Peripheral neuropathy" combined AE term includes the following preferred terms (Pts):
Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy
d "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis

Tabulated summary for combination therapy in MM
The following table is derived from reported data gathered during the multiple myeloma studies with combination therapy. The reported data were not adjusted according to the longer duration of treatment in the Lenalidomide-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies.

Table 2. ADRs reported in clinical studies in patients with multiple myeloma treated with Lenalidomide in combination with bortezomib and dexamethasone, dexamethasone, or melphalan and prednisone

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia◊,◊◊, Upper respiratory tract infection◊, Bacterial, viral and fungal infections (including opportunisticinfections)[◊], Nasopharyngitis, Pharyngitis, Bronchitis[◊], Rhinitis Common Sepsis[◊,◊◊], Lung infection[◊◊], Urinary tract infection[◊◊], Sinusitis[◊]	Common Pneumonia◊,◊◊, Bacterial, viral and fungal infections(including opportunistic infections)[◊], Cellulitis[◊], Sepsis[◊,◊◊], Lung infection[◊◊], Bronchitis[◊], Respiratory tract infection[◊◊], Urinary tract infection[◊◊], Enterocolitis infectious
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basalcellcarcinoma ^,◊, Squamousskin cancer ^,◊,*	Common Acute myeloid leukaemia[◊], Myelodysplastic syndrome[◊], Squamous cell carcinoma of skin ^,◊,** Uncommon T-cell type acute leukaemia[◊], Basal cell carcinoma ^,◊, Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia ^,◊,◊◊, Thrombocytopenia ^,◊,◊◊, Anemia[◊], Haemorrhagic disorder ^, Leucopenias, Lymphopenia Common Febrile neutropenia ^,◊, Pancytopenia[◊] Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia	Very Common Neutropenia ^,◊,◊◊, Thrombocytopenia ^,◊,◊◊, Anemia[◊], Leucopenias, Lymphopenia Common Febrile neutropenia ^,◊, Pancytopenia[◊], Haemolytic anemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity ^	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia[◊,◊◊], Hyperglycaemia, Hypoglycaemia, Hypocalcaemia[◊], Hyponatraemia[◊], Dehydration[◊◊], Decreased appetite[◊◊], Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Hypercalcaemia[+]	Common Hypokalaemia[◊,◊◊], Hyperglycaemia, Hypocalcaemia[◊], Diabetesmellitus[◊], Hypophosphataemia, Hyponatraemia[◊], Hyperuricaemia, Gout, Dehydration[◊◊], Decreased appetite[◊◊], Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies◊◊, Paraesthesia, Dizziness◊◊, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired, Syncope◊◊, Neuralgia, Dysaesthesia	Very Common Peripheral neuropathies◊◊ Common Cerebrovascular accident◊, Dizziness◊◊, Syncope◊◊, Neuralgia Uncommon Intracranial haemorrhage ^, Transient ischaemic attack, Cerebral ischemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation◊,◊◊, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute) ^,◊, Atrial fibrillation◊,◊◊, Congestive cardiac failure◊, Tachycardia, Cardiac failure◊,◊◊, Myocardial ischemia◊
Vascular Disorders	Very Common Venous thromboembolic events ^, predominantly deep vein thrombosis and pulmonary embolism ^,◊,◊◊, Hypotension◊◊ Common Hypertension, Ecchymosis ^	Very Common Venous thromboembolic events ^, predominantly deep vein thrombosisand pulmonary embolism ^,◊,◊◊ Common Vasculitis, Hypotension◊◊, Hypertension Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊,◊◊, Epistaxis ^, Cough Common Dysphonia	Common Respiratory distress◊, Dyspnoea◊,◊◊, Pleuritic pain◊◊, Hypoxia◊◊
Gastrointestinal Disorders	Very Common Diarrhoea◊,◊◊, Constipation◊, Abdominalpain◊◊, Nausea, Vomiting,◊◊, Dyspepsia, Drymouth, Stomatitis Common Gastrointestinal haemorrhage (includingrectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding) ^,◊◊, Dysphagia Uncommon Colitis, Caecitis	Common Gastrointestinal haemorrhage ^,◊,◊◊, Smallintestinal obstruction◊◊, Diarrhoea◊◊, Constipation◊, Abdominal pain◊◊, Nausea, Vomiting◊◊
Hepatobiliary Disorders	Very Common Alanine aminotransferase increased, Aspartate aminotransferase increased Common Hepatocellular injury◊◊, Abnormal liver function tests◊, Hyperbilirubinaemia Uncommon Hepatic failure ^	Common Cholestasis◊, Hepatotoxicity, Hepatocellular injury◊◊, Alanine aminotransferase increased, Abnormal liver function tests◊ Uncommon Hepatic failure ^
Skin and Subcutaneous Tissue Disorders	Very Common Rashes◊◊, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Drug rash with eosinophilia and systemic symptoms◊◊, Skin discolouration, Photosensitivity reaction	Common Rashes◊◊ Uncommon Drug rash with eosinophilia and systemic symptoms◊◊
Musculoskeletal and Connective Tissue Disorders	Very Common Muscular weakness◊◊, Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊), Pain in extremity, Myalgia, Arthralgia◊ Common Joint swelling	Common Muscular weakness◊◊, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊) Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute)◊,◊◊ Common Haematuria ^, Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue◊,◊◊, Oedema (including peripheral oedema), Pyrexia◊,◊◊, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain◊,◊◊, Lethargy	Very Common Fatigue◊,◊◊ Common Oedemaperipheral, Pyrexia◊,◊◊, Asthenia
Investigations	Very Common Blood alkaline phosphatase increased Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion ^	

◊◊ Adverse reactions reported as serious in clinical studies in patients with NDMM who had received Lenalidomide in combination with bortezomib and dexamethasone
^ See section **Adverse drug reactions** description of selected adverse reactions
◊ Adverse reactions reported as serious in clinical studies 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 studies 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 reported data gathered during the main studies in monotherapy for myelodysplastic syndromes and mantle cell lymphoma.

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

^ see section **Adverse drug reactions** description of selected adverse reactions
◊ Adverse events reported as serious in myelodysplastic syndromes clinical studies
~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 Package insert: All ADRs captured by the reported phase 3 study algorithm are included in the Package insert. 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 reported phase 2 study was higher than in the phase 3 study, the event was included in the Package insert at the frequency it occurred in the phase 2 study.
Algorithm applied for myelodysplastic syndromes:
- Reported myelodysplastic syndromes phase 3 study (Reported double-blind safety population, difference between Lenalidomide 5/10mg and placebo by initial dosing regimen occurring in subjects)
  - All treatment-emergent adverse events reported with ≥ 5% of subjects in Lenalidomide and at least 2% difference in proportion between Lenalidomide and placebo
  - All treatment-emergent grade 3 or 4 adverse events reported in 1% of subjects in Lenalidomide and at least 1% difference in proportion between Lenalidomide and placebo
  - All treatment-emergent serious adverse events reported in 1% of subjects in Lenalidomide and at least 1% difference in proportion between Lenalidomide and placebo
- Reported myelodysplastic syndromes phase 2 study
  - All treatment-emergent adverse events reported with ≥ 5% of Lenalidomide treated subjects
  - All treatment-emergent grade 3 or 4 adverse\events reported in 1% of Lenalidomide treated subjects
  - All treatment-emergent serious adverse events reported in 1% of Lenalidomide treated subjects

Table 4. ADRs reported in clinical studies in patients with mantle cell lymphoma treated with Lenalidomide

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

^ see section **adverse drug reactions** description of selected adverse reactions
◊ Adverse events reported as serious in mantle cell lymphoma clinical studies Algorithm applied for mantle cell lymphoma:
- Reported Mantle cell lymphoma controlled phase 2 study
  - All treatment-emergent adverse events reported with ≥ 5% of subjects in Lenalidomide arm and at least 2% difference in proportion between Lenalidomide and control arm
  - All treatment-emergent grade 3 or 4 adverse events reported in ≥1% of subjects in Lenalidomide arm and at least 1.0% difference in proportion between Lenalidomide and control arm
  - All Serious treatment-emergent adverse events reported in ≥1% of subjects in Lenalidomide arm and at least 1.0% difference in proportion between Lenalidomide and control arm
- Reported mantle cell lymphoma single arm phase 2 study
  - All treatment-emergent adverse events reported with ≥ 5% of subjects
  - All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects
  - All Serious treatment-emergent adverse events reported in 2 or more subjects

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

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

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

^ see section **adverse drug reactions** 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 inmonkeys malformations similar to those described with thalidomide (see sections **Pregnancy and Lactation**). 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 reported study 16.4% vs 0.7% in reported study). Treatment- emergent AEs of neutropenia leading to Lenalidomide discontinuation were reported in 2.2% of patients in reported study and 2.4% of patients in reported study. 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 reported study and 0.3% vs 0% in reported study, 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 reported study and 13.0% vs 2.9% in reported study, respectively).

- Newly diagnosed multiple myeloma patients who arenot eligible for transplant receiving Lenalidomide in combination with bortezomib and dexamethasone

Grade 4 neutropenia was reported in the RVd arm to a lesser extent than in the Rd comparator arm (2.7% vs 5.9%) in the reported 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 reported 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 reported 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 reported (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 reported 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 reported 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 reported 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 **Interactions**).

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 **Contraindications, Precautions, Warnings**).
Second primary malignancies

In reported clinical studies 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 reported in clinical studies of newly diagnosed multiple myeloma in patients taking Lenalidomide treatment in combination with melphalan or immediately following HDM/ASCT (see section **Contraindications, Precautions, Warnings).** This increase was not reported in clinical studies 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 **Contraindications, Precautions, Warnings**). The estimated 2-year cumulative risk of progression to AML were reported to be 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 reported 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 reported amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

Hepatic disorders
The following reported 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 reported, some of them when Lenalidomide is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section
Contraindications, Precautions, Warnings,Thyroid disorders).

Tumour flare reaction and tumour lysis syndrome
In reported study, 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 reported study, TLS was reported for one patient in each of the two treatment arms. In the reported supportive study, 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 (see section **Contraindications, Precautions, Warnings**).

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.

Overdose and Treatment[1]
There is no specific experience in the management of Lenalidomide overdose in patients, although in reported dose-ranging studies some patients were exposed to up to 150 mg, and in reported 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.

Storage condition
Store at temperatures not exceeding 30°C

Availability:
Alu/Clear PVC Blister Pack x 7's (box of 21's)

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

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

Important: Immediately seek medical attention at the first sign of adverse drug reaction.

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SUN PHARMA

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