Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

LEDOBOOK

Lenalidomide Capsules 2.5 mg

Lenalidomide Capsules 5 mg

Lenalidomide Capsules 7.5 mg

Lenalidomide Capsules 10 mg

Lenalidomide Capsules 15 mg

Lenalidomide Capsules 20 mg

Lenalidomide Capsules 25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Lenalidomide 2.5 mg.

Each capsule contains Lenalidomide 5 mg.

Each capsule contains Lenalidomide 7.5 mg.

Each capsule contains Lenalidomide 10 mg.

Each capsule contains Lenalidomide 15 mg.

Each capsule contains Lenalidomide 20 mg.

Each capsule contains Lenalidomide 25 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Green opaque cap and Green opaque body size ‘4’, hard gelatin capsule, imprinted with “L2.5” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 14.40 ± 0.40 mm.
- White opaque cap and white opaque body size ‘2’, hard gelatin capsule, imprinted with “L5” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 17.80 ± 0.40 mm.
- White opaque cap and white opaque body size ‘2’, hard gelatin capsule, imprinted with “L7.5” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 17.80 ± 0.40 mm.
- Olive green cap and orange opaque body size ‘0’, hard gelatin capsule, imprinted with “L10” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 21.4 ± 0.40 mm.
- Dark orange opaque cap and dark orange opaque body size ‘0’, hard gelatin capsule, imprinted with “L15” with black ink on the cap, filled with Off-white to pale-yellow Powder, the capsule length is 21.40 ± 0.40 mm.
- Orange opaque cap and orange opaque body size ‘0’, hard gelatin capsule,

imprinted with “L20” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 21.40 ± 0.40 mm.

- White opaque cap and white opaque body size ‘0’, hard gelatin capsule, imprinted with “L25” with black ink on the cap, filled with Off-white to pale- yellow Powder, the capsule length is 21.40 ± 0.40 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

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

Lenalidomide Capsules as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Lenalidomide Capsules 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 Capsules 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 Capsules as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

Follicular lymphoma

Lenalidomide in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

4.2 Posology and method of administration

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

For all indications described below:

• Dose is modified based upon clinical and laboratory findings (see section 4.4).

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

• In case of neutropenia, the use of growth factors in patient management should be considered.

• If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Posology

Newly diagnosed multiple myeloma (NDMM)

• Lenalidomide in combination with dexamethasone until disease progression in patients who are not eligible for transplant

Lenalidomide treatment must not be started if the ANC is < 1.0 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 > day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

• *Neutropenia*

When neutrophils	Recommended course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment

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

[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 Section 5.1 and the corresponding Summary of Product Characteristics.

Up to eight 21-day treatment cycles (24 weeks of initial treatment) are recommended.

Continued treatment: Lenalidomide in combination with dexamethasone until progression

Continue lenalidomide 25 mg orally once daily on days 1-21 of repeated 28-day cycles in combination with dexamethasone. Treatment should be continued until disease progression or unacceptable toxicity.

• *Dose reduction steps*

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

Dose level- 4	5 mg
Dose level -5	2.5 mg

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

• *Thrombocytopenia*

When platelets	Recommended course
Fall to < 30 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.

• <u>Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)</u>

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

Follicular lymphoma (FL)

Lenalidomide treatment must not be started if the ANC is < 1 x 10^9/L, and/or platelet count < 50 x 10^9/L, unless secondary to lymphoma infiltration of bone marrow.

Recommended dose

The recommended starting dose of lenalidomide is 20 mg, orally once daily on days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m2 intravenously (IV) every week in Cycle 1 (days 1, 8, 15, and 22) and day 1 of every 28-day cycle for cycles 2 through 5.

Dose reduction steps

Starting dose	20 mg once daily on days 1-21, every 28 days
Dose Level -1	15 mg once daily on days 1-21, every 28 days
Dose Level -2	10 mg once daily on days 1-21, every 28 days
Dose Level -3	5 mg once daily on days 1-21, every 28 days

For dose adjustments due to toxicity with rituximab, refer to the corresponding summary of product characteristics.

Thrombocytopenia

When platelets	Recommended course
Falls to < 50 x 10^9/ L	Interrupt lenalidomide treatment and conduct CBC atleast every 7 days
Returns to ≥ 50 x 10^9/ L	Resume at next lower dose level (dose level -1)
For each subsequent drop below 50 x 10^9/L Returns to ≥ 50 x 10^9/L	Interrupt lenalidomide treatment and conduct CBC atleast every 7 days Resume lenalidomide at next lower dose level (doselevel -2, -3). Do not dose below dose level -3.

Neutropenia

When ANC	Recommended course [a]
Falls < 1.0 x 10^9/L for at least 7 days or Falls to < 1.0 x 10^9 /L with associated fever (body temperature≥ 38.5°C) or Falls to < 0.5 x 10^9 /L	Interrupt lenalidomide treatment and conduct CBC atleast every 7 days
Returns to ≥ 1.0 x 10^9 /L	Resume lenalidomide at next lower dose level (doselevel -1)

For each subsequent drop below 1.0 x 10^9 /L for at least 7days or drop to < 1.0 x 10^9 /L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9 /L Returns to ≥1.0 x 10^9 /L	Interrupt lenalidomide treatment and conduct CBC atleast every 7 days Resume lenalidomide at next lower dose level (doselevel -2, -3). Do not dose below dose level-3

[a] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF

Mantle cell lymphoma (MCL) or follicular lymphoma (FL)

Tumour lysis syndrome (TLS)

All patients should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or for a longer period if clinically indicated. To monitor for TLS,patients should have a chemistry panel drawn weekly during the first cycle and as clinically indicated.

Lenalidomide may be continued (maintain dose) in patients with laboratory TLS or Grade 1 clinical TLS, or at thephysician's discretion, reduce dose by one level and continue lenalidomide. Vigorous intravenous hydration should beprovided and appropriate medical management according to the local standard of care, until correction of electrolyteabnormalities. Rasburicase therapy may be needed to reduce hyperuricaemia. Hospitalisation of the patient will be atphysician's discretion.

In patients with Grade 2 to 4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinicallyindicated. Vigorous intravenous hydration should be provided and appropriate medical management according to thelocal standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalisation will be atphysician's discretion. When the TLS resolves to Grade 0, restart lenalidomide at next lower dose per physician'sdiscretion (see section 4.4).

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 treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR (see section 4.4).

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 Capsules should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 5.1).

• Elderly

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials 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 (see section 5.1).

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 4.4).

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 observed 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 observed 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 observed between patients aged 65 years or over compared with patients aged under 65 years of age.

Follicular lymphoma

For follicular lymphoma patients treated with lenalidomide in combination with rituximab, the overall rate of adverse events is similar for patients aged 65 years or over compared with patients under 65 years of age. No overall difference in efficacy was observed between the two age groups.

• 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 4.4). 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 trial experiences 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.

Follicular lymphoma

Renal function (CLcr)	Dose adjustment (days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 60 mL/min)	10 mg once daily [1, 2]

Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	No data available [3]
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	No data available [3]

1 The dose may be escalated to 15 mg once daily after 2 cycles if the patient has tolerated therapy.
[2] For patients on a starting dose of 10 mg, in case of dose reduction to manage Grade 3 or 4 neutropenia orthrombocytopenia, or other Grade 3 or 4. Toxicity judged to be related to lenalidomide do not dose below 5 mg everyother day or 2.5 mg once daily.
[3] Patients with severe renal impairment or ESRD were excluded from study.
After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should bebased on individual patient treatment tolerance, as described above.
• Patients with hepatic impairment

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

Method of administration

Oral use.

Lenalidomide Capsules 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.

4.3 Contraindications
• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Women who are pregnant.

• Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use
When lenalidomide is given in combination with other medicinal products, the corresponding Summary of Product Characteristics must be consulted prior to initiation of treatment.

Pregnancy warning

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

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

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 demonstrated 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 5.2). 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 Capsules or shortly after he has stopped taking Lenalidomide Capsules, 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 4.5). 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 4.5).

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

According to local practice, 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 4.5 and 4.8).

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

Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with lenalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during Lenalidomide therapy.

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 4.2).

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

Overall, grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively). Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reduction may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance arms compared to the placebo maintenance arms in studies evaluating lenalidomide maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

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

Grade 4 neutropenia was observed at a lower frequency in the lenalidomide in combination with bortezomib and dexamethasone (RVd) arm compared to the Rd comparator arm (2.7% vs 5.9%) in the SWOG S0777 study. Grade 4 febrile neutropenia was reported at similar frequencies in the RVd arm and Rd arm (0.0% vs 0.4%). Patients

should be advised to promptly report febrile episodes; a treatment interruption and/or dose reduction may be required (see section 4.2).

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the RVd arm compared to the Rd comparator arm (17.2 % vs 9.4%).

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

Grade 4 neutropenia was observed in the lenalidomide arms in combination with dexamethasone to a lesser extent than in the comparator arm (8.5% in the Rd [continuous treatment] and Rd18 [treatment for 18 four-week cycles] compared with 15% in the melphalan/prednisone/thalidomide arm, see section 4.8). Grade 4 febrile neutropenia episodes were consistent with the comparator arm (0.6 % in the Rd and Rd18 lenalidomide/dexamethasone-treated patients compared with 0.7% in the melphalan/prednisone/thalidomide arm, see section 4.8).

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

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

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

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

• Multiple myeloma: patients with at least one prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least one prior therapy is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/ dexamethasone-treated patients; see section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; see section 4.8).

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; see section 4.8).

• Myelodysplastic syndromes

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

• Mantle cell lymphoma

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

•Follicular lymphoma

The combination of lenalidomide with rituximab in follicular lymphoma patients is associated with a higher incidence ofGrade 3 or 4 neutropenia compared with patients on the placebo/rituximab arm. Febrile neutropenia and Grade 3 or 4thrombocytopenia were more commonly observed in the lenalidomide/ rituximab arm (see section 4.8).

Thyroid disorders

Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy.

There was no increase in peripheral neuropathy observed with lenalidomide in combination with dexamethasone or melphalan and prednisone or lenalidomide monotherapy or with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

The combination of lenalidomide with intravenous bortezomib and dexamethasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. The frequency was lower when bortezomib was administered subcutaneously. For additional information, see Section 4.8 and the SmPC for bortezomib.

Tumour flare reaction and tumour lysis syndrome

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide, and no reports in patients with MDS treated with lenalidomide.

•*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 studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, NSAIDs and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (see sections 4.2 and 4.8).

•*Follicular lymphoma*

Careful monitoring and evaluation for TFR is recommended. Tumour flare may mimic PD. Patients who experienced Grade 1 and 2 TFR were treated with corticosteroids, NSAIDs and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of theindividual patient (see sections 4.2 and 4.8).

Careful monitoring and evaluation for TLS is recommended. Patients should be well hydrated and receive TLSprophylaxis, in addition to weekly chemistry panels during the first cycle or longer, as clinically indicated (see sections4.2 and 4.8).

Tumour burden

• Mantle cell lymphoma

Lenalidomide is not recommended for the treatment of patients with high tumour burden if alternative treatment options are available.

Early death

In study MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, there were 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (40%) and 6/28 (21%) (See section 5.1).

Adverse events

In study MCL-002, during treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).

Patients with high tumour burden should therefore be closely monitored for adverse reactions (see Section 4.8) including signs of tumour flare reaction (TFR). Please refer to section 4.2 for dose adjustments for TFR.

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

Lactose intolerance

Lenalidomide Capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Second primary malignancies

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

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and

prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).
In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).
A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).
In newly diagnosed multiple myeloma patients receiving lenalidomide in combination with bortezomib and dexamethasone, the hematologic SPM incidence rate was 0.00 – 0.16 per 100 person-years and the incidence rate of solid tumour SPM 0.21 – 1.04 per 100 person-years.
The increased risk of secondary primary malignancies associated with lenalidomide is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Lenalidomide Capsules 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 clinical trials 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 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 present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a

post-hoc analysis of a clinical trial of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (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 4.8)

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.

Second primary malignancies in follicular lymphoma

In a relapsed/refractory iNHL study which included follicular lymphoma patients, no increased risk of SPMs in thelenalidomide/rituximab arm, compared to the placebo/ rituximab arm, was observed. Hematologic SPM of AML occurredin 0.29 per 100 person-years in the lenalidomide/rituximab arm compared with 0.29 per 100 person-years in patientsreceiving placebo/rituximab. The incidence rate of hematologic plus solid tumour SPMs (excluding non-melanoma skincancers) was 0.87 per 100 person-years in the lenalidomide/rituximab arm, compared to 1.17 per 100 person-years inpatients receiving placebo/rituximab with a median follow-up of 30.59 months (range 0.6 to 50.9 months).

Non-melanoma skin cancers are identified risks and comprise squamous cell carcinomas of skin or basal cellcarcinomas.

Physicians should monitor patients for the development of SPMs. Both the potential benefit of lenalidomide and the riskof SPMs should be considered when considering treatment with lenalidomide.

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 observed with lenalidomide in combination with dexamethasone than with MPT in patients with NDMM who are not eligible for transplant, and with lenalidomide maintenance compared to placebo in patients with

NDMM who had undergone ASCT. Grade ≥ 3 infections occurred within the context of neutropenia in less than one-third of the patients. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (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

There was a higher rate of intolerance (grade 3 or 4 adverse events, serious adverse events, discontinuation) 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 4.2 and 4.8).

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.

4.5 Interaction with other medicinal products and other forms of interaction
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 4.4 and 4.8).

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an *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 be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

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 increased 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.

4.6 Fertility, pregnancy and lactation

Due to the teratogenic potential, lenalidomide must be prescribed under a Pregnancy Prevention Programme (see section 4.4) unless there is reliable evidence that the patient does not have childbearing potential.

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 should be 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 5.2). 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.

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 4.3).

Breast-feeding

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

Fertility

A 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.

4.7 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.

4.8 Undesirable effects

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 CALGB 100104. 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 occurred after the start of maintenance treatment suggests that the frequencies described in Table 1 may be higher than actually observed during the maintenance treatment period. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

The serious adverse reactions observed more frequently (≥5%) with lenalidomide maintenance than placebo were:

• Pneumonias (10.6%; combined term) from IFM 2005-02

• Lung infection (9.4% [9.4% after the start of maintenance treatment]) from CALGB 100104

In the IFM 2005-02 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 CALGB 100104 study, the adverse reactions observed 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 SWOG S0777 study, the serious adverse reactions observed 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 observed 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 observed 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 observed 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 observed 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 observed 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 two phase 3 placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/ dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/ dexamethasone than placebo/dexamethasone combination were:

• Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)

• Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) 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 data from a total of 286 patients from one phase 2 study and one phase 3 study (see section 5.1). In the phase 2, all 148 patients were on lenalidomide treatment. In the phase 3 study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were 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 4.4)

• Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

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 data from 254 patients from a phase 2 randomised, controlled study MCL-002 (see section 5.1).

Additionally, adverse drug reactions from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in study MCL-002 (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 observed adverse reactions which occurred more frequently in the lenalidomide arm compared with the control arm in study MCL-002 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 MCL-002 there was overall an apparent increase in early (within 20 weeks) deaths. Patients with high tumour burden at baseline are at increased risk of early death, 16/81 (20%) early deaths in the lenalidomide arm and 2/28 (7%) early deaths in the control arm. Within 52 weeks corresponding figures were 32/81 (39.5%) and 6/28 (21%) (see section 5.1).

During treatment cycle 1, 11/81 (14%) patients with high tumour burden were withdrawn from therapy in the lenalidomide arm vs. 1/28 (4%) in the control group. The main reason for treatment withdrawal for patients with high tumour burden during treatment cycle 1 in the lenalidomide arm was adverse events, 7/11 (64%).

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

Follicular lymphoma

The overall safety profile of lenalidomide in combination with rituximab in patients with previously treated follicularlymphoma is based on data from 294 patients from a Phase 3 randomised, controlled study NHL-007. Additionally,adverse drug reactions from supportive study NHL-008 have been included.

The serious adverse reactions observed most frequently (with a difference of at least 1 percentage point) in study NHL-007 in the lenalidomide/rituximab arm compared with the placebo/rituximab arm were:

• Febrile neutropenia (2.7%)
• Pulmonary embolism (2.7%)
• Pneumonia (2.7%)

In the NHL-007 study the adverse reactions observed more frequently in the lenalidomide/rituximab arm compared withthe placebo/rituximab arm (with at least 2% higher frequency between arms) were neutropenia (58.2%), diarrhoea(30.8%), leucopenia (28.8%), constipation (21.9%), cough (21.9%) and fatigue (21.9%).

Tabulated list of adverse reactions

The adverse reactions observed 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 data).
Adverse reactions have been included under the appropriate category in the table below according to the highest frequency observed in any of the main clinical trials.

Tabulated summary for monotherapy in MM
The following table is derived from data gathered during NDMM studies in patients who have undergone ASCT treated with lenalidomide maintenance. The 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 (see section 5.1).

Table 1. ADRs reported in clinical trials 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,
Nervous System Disorders	Very Common Paraesthesia Common Peripheral neuropathyc	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 trials in patients with NDMM who had undergone ASCT

* Applies to serious adverse drug reactions only

^ See section 4.8 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 data gathered during the multiple myeloma studies with combination therapy. The 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 (see section 5.1).

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 opportunistic infections)◊, 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 Basal cell carcinoma^,◊, Squamous skin 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◊, Diabetes mellitus◊, 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 thrombosis and 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◊, Abdominal pain◊◊, Nausea, Vomiting◊◊, Dyspepsia, Dry mouth, Stomatitis Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^,◊◊, Dysphagia Uncommon Colitis, Caecitis	Common Gastrointestinal haemorrhage^,◊,◊◊, Small intestinal 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	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	Common Muscular weakness◊◊, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊,◊◊) Uncommon
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 Oedema peripheral, Pyrexia◊,◊◊, Asthenia
Investigations	Very Common Blood alkaline phosphatase increased Common	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

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

^See section 4.8 description of selected adverse reactions

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

+ Applies to serious adverse drug reactions only

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

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

Tabulated summary from monotherapy

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

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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs / Frequency
Infections and Infestations	Very Common 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
Endocrine Disorders	Very Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Decreased appetite Common Iron overload, Weight	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
Skin and Subcutaneous Tissue	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,	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 4.8 description of selected adverse reactions
◊ Adverse events reported as serious in myelodysplastic syndromes clinical trials
~Altered mood was reported as a common serious adverse event in the myelodysplastic syndromes phase 3 study; it was not reported as a grade 3 or 4 adverse event
Algorithm applied for inclusion in the SmPC: All ADRs captured by the phase 3 study algorithm are included in the EU SmPC. For these ADRs, an additional check of the

frequency of the ADRs captured by the phase 2 study algorithm was undertaken and, if the frequency of the ADRs in the phase 2 study was higher than in the phase 3 study, the event was included in the EU SmPC at the frequency it occurred in the phase 2 study.

Algorithm applied for myelodysplastic syndromes:

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

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

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

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

• Myelodysplastic syndromes phase 2 study

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

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

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

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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)◊, Nasopharyngitis, Pneumonia◊ Common	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 and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydration◊	Common Dehydration◊, Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	

Nervous System Disorders	Common Dysgeuesia, 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^,◊,
Respiratory, Thoracic and Mediastinal	Very Common Dyspnoea◊	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Diarrhoea◊, Nausea◊, Vomiting◊, Constipation Common Abdominal pain◊	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness◊	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
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	Common Pyrexia◊, Asthenia◊, Fatigue

^see section 4.8 description of selected adverse reactions

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

• Mantle cell lymphoma controlled phase 2 study

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

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

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

• Mantle cell lymphoma single arm phase 2 study

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

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

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

Tabulated summary of post-marketing adverse reactions

The following table is derived from data gathered during the main studies (NHL-007 and NHL-008) using lenalidomide incombination with rituximab for patients with follicular lymphoma.

Table 5: ADRs reported in clinical trials in patients with follicular lymphoma treated with lenalidomide incombination with rituximab

System Organ Class / Preferred Term	**All ADRs/Frequency**	**Grade 3−4 ADRs / Frequency**
Infections and Infestations	Very Common Upper respiratory tract infection Common Pneumonia◊, Influenza, Bronchitis, Sinusitis, Urinary	Common Pneumonia◊, Sepsis◊, Lung infection, Bronchitis, Gastroenteritis, Sinusitis, Urinary tract infection, Cellulitis ◊
Neoplasms Benign,Malignant and Unspecified(incl cysts and polyps)	Very Common Tumour flare^ Common Squamous Cell Carcinoma of Skin◊,^,+	Common Basal cell carcinoma^ ,◊
Blood and LymphaticSystem Disorders	Very Common Neutropenia^,◊, Anaemia◊,Thrombocytopenia^, Leucopenia** Lymphopenia***	Very Common Neutropenia^,◊ Common Anaemia◊, Thrombocytopenia^, Febrileneutropenia◊, Pancytopenia,Leucopenia**, Lymphopenia***

Metabolism and Nutrition Disorders	Very Common Decreased appetite, Hypokalaemia Common Hypophosphataemia, Dehydration	Common Dehydration, Hypercalcaemia◊, Hypokalaemia, Hypophosphataemia, Hyperuricaemia
Psychiatric Disorders	Common Depression, Insomnia	
Nervous System Disorders	Very Common Headache, Dizziness Common Peripheral sensory neuropathy, Dysgeusia	Common Syncope
Cardiac Disorders	Uncommon Arrhythmia◊	
Vascular Disorders	Common Hypotension	Common Pulmonary embolism^,◊, Hypotension
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea◊, Cough, Common Oropharyngeal pain,	Common Dyspnoea◊
Gastrointestinal Disorders	Very Common Abdominal pain◊, Diarrhoea, Constipation, Nausea, Vomiting, Dyspepsia Common Upper abdominal pain, Stomatitis, Drymouth	Common Abdominal pain◊, Diarrhoea, Constipation, Stomatitis
Skin and Subcutaneous Tissue Disorders	Very Common Rash*, Pruritus Common Dry skin, Night sweats,	Common Rash*, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain, Arthralgia Common Pain in extremity, Muscular weakness, Musculoskeletal pain, Myalgia, Neck pain	Common Muscular weakness, Neck pain
Renal and Urinary Disorders		Common Acute kidney injury◊

General Disorders and Administration Site Conditions	Very Common Pyrexia, Fatigue, Asthenia, Peripheraloedema Common Malaise, Chills	Common Fatigue, Asthenia
Investigations	Very Common Alanine aminotransferase increased Common Weight decreased, Blood Bilirubin increased	

^see section 4.8 description of selected adverse reactions

Algorithm applied for follicular lymphoma:

Controlled– Phase 3 trial:
o NHL-007 ADRs- All treatment-emergent AEs with ≥ 5.0% of subjects in lenalidomide/ rituximab arm and at least 2.0%higher frequency (%) in Len arm compared to control arm - (Safety population)
o NHL-007 Gr 3/4 ADRs- All Grades 3 or Grade 4 treatment-emergent AEs with at least 1.0% subjects inlenalidomide/rituximab arm and at least 1.0% higher frequency in lenalidomide arm compared to control arm - (safetypopulation)
o NHL-007 Serious ADRs- All serious treatment-emergent AEs with at least 1.0% subjects in lenalidomide/rituximab armand at least 1.0% higher frequency in lenalidomide/rituximab arm compared to control arm - (safety population)
FL single arm - phase 3 trial:
o NHL-008 ADRs- All treatment-emergent adverse events with ≥ 5.0% of subjects
o NHL-008 Gr 3/4 ADRs- All Grade 3/4 treatment-emergent adverse events reported in ≥ 1.0% of subjects
o NHL-008 Serious ADRs- All serious treatment-emergent adverse events reported in ≥ 1.0% of subjects
◊ Adverse events reported as serious in follicular lymphoma clinical trials

Table 6. ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class / Preferred	**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
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
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

^see section 4.8 description of selected adverse reactions

Description of selected adverse reactions

Teratogenicity

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

Neutropenia and thrombocytopenia

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

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 4 neutropenia compared to placebo maintenance (32.1% vs 26.7% [16.1% vs 1.8% after the start of maintenance treatment] in CALGB 100104 and 16.4% vs 0.7% in IFM 2005-02, respectively). Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported in 2.2% of patients in CALGB 100104 and 2.4% of patients in IFM 2005-02, respectively. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively).
Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 3 or 4 thrombocytopenia compared to placebo maintenance (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively).

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

Grade 4 neutropenia was observed in the RVd arm to a lesser extent than in the Rd comparator arm (2.7% vs 5.9%) in the SWOG S0777 study. Grade 4 febrile neutropenia was reported at similar frequencies in the RVd arm compared to the Rd arm (0.0% vs 0.4%).
Grade 3 or 4 thrombocytopenia was observed in the RVd arm to a greater extent than in the Rd comparator arm (17.2 % vs 9.4%).

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

The combination of lenalidomide with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 4 neutropenia (8.5% in Rd and Rd18, compared with MPT (15%). Grade 4 febrile neutropenia was observed infrequently (0.6% in Rd and Rd18 compared with 0.7% in MPT).
The combination of lenalidomide with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18) compared with MPT (11%).

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

The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of grade 4 neutropenia (34.1% in MPR+R/MPR+p) compared with MPp+p (7.8%). There was a higher frequency of grade 4 febrile neutropenia observed (1.7% in MPR+R/MPR+p compared to 0.0% in MPp+p).
The combination of lenalidomide with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of grade 3 and grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

• Multiple myeloma: patients with at least one prior therapy

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

(0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/ dexamethasone treated patients).
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients).

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

• Mantle cell lymphoma patients
In mantle cell lymphoma patients, lenalidomide is associated with a higher incidence of grade 3 or 4 neutropenia (43.7% in lenalidomide-treated patients compared with 33.7% in patients in the control arm in the phase 2 study). Grade 3 or 4 febrile neutropenia episodes were observed in 6.0% of lenalidomide-treated patients compared with 2.4% in patients on control arm.

Venous thromboembolism
An increased risk of DVT and PE is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with lenalidomide in combination with melphalan and prednisone or in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma treated with lenalidomide monotherapy (see section 4.5).
Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

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

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

Allergic reactions and severe skin reactions
Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS,TEN and DRESS have been reported with the use of lenalidomide. A possible cross-reaction between lenalidomide andthalidomide has been reported in the literature. Patients with a history of severe rash associated with thalidomidetreatment should not receive lenalidomide (see section 4.4).

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

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

• Myelodysplastic syndromes
Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4). The estimated 2-year cumulative risk of progression to AML were 13.8% in patients with an isolated Del (5q) abnormality compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.
In a post-hoc analysis of a clinical trial of lenalidomide in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity and 3.6% in patients with IHC-p53 negativity (p=0.0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11.1%) compared to a non-responder (34.8%).

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

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

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

Tumour flare reaction and tumour lysis syndrome
In study MCL-002, approximately 10% of lenalidomide-treated patients experienced TFR compared to 0% in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10% of subjects experienced TFR; all report were Grade 1 or 2

in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. There were no reports of TLS in study MCL-001 (see section 4.4).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA.**

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

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.
Mechanism of action
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 haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.

Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.

The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells.
The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with lenalidomide in all subsets of the paediatric population in multiple myeloma,

myelodysplastic syndromes and mantle cell lymphoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

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

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

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

Distribution

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

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

Biotransformation and elimination

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

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and

OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

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

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

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

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

Older people

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

Renal impairment

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

Hepatic impairment

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

Other intrinsic factors

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Anhydrous
Cellulose Microcrystalline
Croscarmellose Sodium
Magnesium stearate
Gelatin
Titanium dioxide
Black iron oxide
Potassium hydroxide
Shellac
The 10 mg, 15 mg and 20 mg capsule shell contains iron oxide red.
The 2.5 mg, 10 mg and 20 mg capsule shell contains iron oxide yellow.
The 2.5 mg and 10 mg capsule shell contains FD&C blue 2.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Clear PVC/Aclar - Aluminium foil blister pack.

Lenalidomide Capsules 2.5 mg/ 5 mg/ 7.5 mg/ 10 mg/ 15 mg/ 20 mg/ 25 mg

Blister pack of 21 capsules (3X7's).

6.6. Special precautions for disposal and other handling

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

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500 038,
Telangana State, India.

Manufactured by:
Eugia Pharma Specialities Limited,
Survey No. 550, 551 & 552, Kolthur Village,

Shamirpet Mandal,
Medchal-Malkajgiri District, Telangana,
India.

8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0452

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

07th October, 2022

10. DATE OF REVISION OF THE TEXT