SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lenalidomide Zentiva 15 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 15 mg lenalidomide.

Excipients with known effect:

Each capsule contains 199.3 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule.

Opaque white body and opaque blue to light blue cap, with a length of approximately 21.7 mm, marked “L9NL” and “15”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma

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

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

Lenalidomide in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes

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

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

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 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 absolute neutrophil count (ANC) is $< 1.0\times10^9$/L, and/or platelet counts are $< 50 \times10^9$/L.

Recommended dose
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 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[1]	**Dexamethasone**[1]
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

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

- Thrombocytopenia

When platelets	**Recommended course**
Falls to < 25×10^9/L	Stop lenalidomide dosing for remainder of cycle[1]
Returns to ≥ 50×10^9/L	Decrease by 1 dose level when dosing resumed at next cycle

[1] 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.

- ANC - neutropenia

When ANC	**Recommended course[1]**
First falls to < 0.5×10^9/L Returns to ≥ 1×10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5×10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily.

[1] 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 haematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no haematologic toxicity for at least 2 consecutive cycles: ANC ≥ 1.5×10^9/L with a platelet count ≥ 100×10^9/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 < 1.0×10^9/L, and/or platelet counts are < 50×10^9/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/m2 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 (SmPC).

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[1]
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

[1] Dose reduction for all products can be managed independently.

- Thrombocytopenia

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

- ANC – neutropenia

When ANC	**Recommended course**[1]
First falls to < 0.5×10^9/L Returns to ≥ 1×10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5×10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily

[1] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add 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 < 1.5×10^9/L, and/or platelet counts are < 75×10^9/L.

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

- Dose reduction steps

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[1]	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	NA	0.25 mg/kg

[1] If neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide.

- Thrombocytopenia

When platelets	Recommended course
First falls to $< 25\times10^9$/L Returns to $\geq 25\times10^9$/L	Interrupt lenalidomide treatment Resume lenalidomide and melphalan at dose level -1 once daily
For each subsequent drop $< 30\times10^9$/L Returns to $\geq 30\times10^9$/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily.

- ANC – neutropenia

When ANC	Recommended course[1]
First falls to $< 0.5\times10^9$/L Returns to $\geq 0.5\times10^9$/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns to $\geq 0.5\times10^9$/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop $< 0.5\times10^9$/L Returns to $\geq 0.5\times10^9$/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily

[1] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide.

Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the ANC is $< 1.0\times10^9$/L, and/or platelet counts are $< 75\times10^9$/L.

Recommended dose

The recommended starting dose is lenalidomide 10 mg orally once daily continuously (on days 1-28 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)[1]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (days 1-21 every 28 days)	5 mg

Dose level -3	NA	5 mg (days 1-21 every 28 days)
	Do not dose below 5 mg (days 1-21 every 28 days)	

[1] After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

- Thrombocytopenia

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

- ANC – neutropenia

When ANC	**Recommended course[1]**
Falls to < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level once daily

[1] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide.

Multiple myeloma with at least 1 prior therapy

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

Recommended dose

The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1-21 of repeated 28 - day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1-4, 9-12, and 17-20 of each 28 - day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 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

	Lenalidomide
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 falls to < 30×10^9/L Returns to ≥ 30×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 30×10^9/L Returns to ≥ 30×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2 or -3) once daily

	Do not dose below 5 mg once daily

- ANC – neutropenia

When ANC	**Recommended course**[1]
First falls to < 0.5×10^9/L Returns to ≥ 0.5×10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Returns to ≥ 0.5×10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level -1 once daily
For each subsequent drop < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) once daily Do not dose below 5 mg once daily

[1] At the physician's discretion, if neutropenia is the only toxicity at any dose level, add G-CSF and maintain the dose level of lenalidomide.

Myelodysplastic syndromes (MDS)

Lenalidomide treatment must not be started if the ANC < 0.5×10^9/L and/or platelet counts < 25×10^9/L.

Recommended dose

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1 – 21 of repeated 28-day cycles.

- Dose reduction steps

	Lenalidomide
Starting dose	10 mg once daily on days 1 – 21 every 28 days
Dose level -1	5 mg once daily on days 1 – 28 every 28 days
Dose level -2	2.5 mg once daily on days 1 – 28 every 28 days
Dose level -3	2.5 mg every other day 1 – 28 every 28 days

- Thrombocytopenia

When platelets	**Recommended course**
Falls to < 25×10^9/L Returns to ≥ 25×10^9/L – < 50×10^9/L on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50×10^9/L at any time	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) once daily

- ANC – neutropenia

When ANC	**Recommended course**
First falls to < 0.5×10^9/L Returns to ≥ 0.5×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) once daily

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 1 g/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 – 21 of repeated 28-day cycles.

- Dose reduction steps

	Lenalidomide
Starting dose	25 mg once daily on days 1 – 21 every 28 days
Dose level -1	20 mg once daily on days 1 – 21 every 28 days
Dose level -2	15 mg once daily on days 1 – 21 every 28 days
Dose level -3	10 mg once daily on days 1 – 21 every 28 days
Dose level -4	5 mg once daily on days 1 – 21 every 28 days
Dose level -5	2.5 mg once daily on days 1 – 21 every 28 days[1] 5 mg every other day on days 1 – 21 every 28 days

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

- Thrombocytopenia

When platelets	**Recommended course**
Falls to < 50×10^9/L	Interrupt lenalidomide treatment and conduct complete blood count (CBC) at least every 7 days
Returns to ≥ 60×10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop < 50×10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Returns to ≥ 60×10^9/L	Resume lenalidomide at next lower dose level (dose level -2, -3, -4 or -5) Do not dose below dose level -5

- ANC – neutropenia

When ANC	**Recommended course**
First falls to < 1×10^9/L for at least 7 days or falls to < 1×10^9/L with associated fever (body temperature ≥ 38.5°C) or falls to < 0.5×10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Returns to ≥ 1×10^9/L	Resume lenalidomide at next lower dose level (dose level -1)
For each subsequent drop < 1×10^9/L for at least 7 days or drop to < 1×10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5×10^9/L Returns to ≥ 1×10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -2, -3, -4, -5) Do not dose below dose level -5

Follicular lymphoma (FL)

Lenalidomide treatment must not be started if the ANC is < 1×10^9/L, and/or platelet count < 50×10^9/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 1-21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/m^2 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

	Lenalidomide
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 SmPC.

- Thrombocytopenia

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

- ANC – neutropenia

When ANC	**Recommended course** [1]
Falls to < 1×10^9/L for at least 7 days or falls to < 1×10^9/L with associated fever (body temperature ≥ 38.5°C) or falls to < 0.5×10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days
Returns to ≥ 1×10^9/L	Resume lenalidomide at next lower dose level (dose level -1) once daily
For each subsequent drop < 1×10^9/L for at least 7 days or drop to < 1×10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5×10^9/L	Interrupt lenalidomide treatment and conduct CBC at least every 7 days
Returns to ≥ 1×10^9/L	Resume lenalidomide at next lower dose level (dose level -2, -3) once daily Do not dose below dose level -3

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

<u>MCL or FL</u>
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 the physician's discretion, reduce dose by 1 level and continue lenalidomide. Vigorous IV hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy may be needed to reduce hyperuricaemia. Hospitalisation of the patient will be at physician's discretion. In patients with grade 2-4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinically indicated. Vigorous IV hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalisation will be at physician's discretion. When the TLS resolves to grade 0, restart lenalidomide at next lower dose per physician's discretion (see section 4.4).

Tumour flare reaction (TFR)
At the physician's discretion, lenalidomide may be continued in patients with grade 1 or 2 TFR without interruption or modification. At the physician's discretion, therapy with non-steroidal anti-inflammatory drugs (NSAIDs), limited duration corticosteroids, and/or narcotic analgesics may be administered. In patients with grade 3 or 4 TFR, withhold treatment with lenalidomide and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤ grade 1, restart lenalidomide treatment at the same dose level for the rest of the cycle. 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, anaphylactic reaction, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions.

Special populations

Paediatric population
Lenalidomide should not be used in children and adolescents from birth to less than 18 years because of safety concerns (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 MDS patients up to 95 years of age and in MCL 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.

NDMM: Patients who are not eligible for transplant

Patients with NDMM 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 NDMM 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 NDMM 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 1 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.

MDS

For MDS patients treated with lenalidomide, no overall difference in safety and efficacy was observed between patients aged over 65 and younger patients.

MCL

For MCL 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.

FL
For FL 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 2 age groups.

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, MDS, MCL or FL. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease. There are no phase III trial experiences with end stage renal disease (ESRD) (Cl_{Cr} < 30 mL/min, requiring dialysis).

- *Multiple myeloma*

Renal function (Cl_{Cr})	**Dose adjustment**
Moderate renal impairment ($30 \leq Cl_{Cr} < 50$ mL/min)	10 mg once daily[1]
Severe renal impairment ($CL_{Cr} < 30$ mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day
ESRD ($CL_{Cr} < 30$ 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.

- *MDS*

Renal function (Cl_{Cr})	**Dose adjustment**	
Moderate renal impairment ($30 \leq Cl_{Cr} < 50$ mL/min)	Starting dose	5 mg once daily on days 1 – 21 of repeated 28-day cycles
	Dose level -1[1]	2.5 mg once daily on days 1 – 28 of repeated 28-day cycles
	Dose level -2[1]	2.5 mg once every other day on days 1 – 28 of repeated 28-day cycles
Severe renal impairment ($Cl_{Cr} < 30$ mL/min, not requiring dialysis)	Starting dose	2.5 mg once daily on days 1 – 21 of repeated 28-day cycles
	Dose level -1[1]	2.5 mg every other day on days 1 – 28 of repeated 28-day cycles
	Dose level -2[1]	2.5 mg twice a week on days 1 – 28 of repeated 28-day cycles
ESRD ($Cl_{Cr} < 30$ mL/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis	Starting dose	2.5 mg once daily on days 1 – 21 of repeated 28-day cycles
	Dose level -1[1]	2.5 mg every other day on days 1 – 28 of repeated 28-day cycles
	Dose level -2[1]	2.5 mg twice a week on days 1 – 28 of repeated 28-day cycles

[1] 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.

- *MCL*

Renal function (Cl_{Cr})	**Dose adjustment** on days 1 – 21 of repeated 28-day cycles

Moderate renal impairment ($30 \leq Cl_{Cr} < 50$ mL/min)	10 mg once daily[1]
Severe renal impairment ($Cl_{Cr} < 30$ mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day
ESRD ($Cl_{Cr} < 30$ 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.

- *FL*

Renal function (Cl_{Cr})	**Dose adjustment** on days 1 - 21 of repeated 28-day cycles
Moderate renal impairment ($30 \leq Cl_{Cr} < 60$ mL/min)	10 mg once daily[1,2]
Severe renal impairment ($Cl_{Cr} < 30$ mL/min, not requiring dialysis)	5 mg once daily
ESRD ($Cl_{Cr} < 30$ 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 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 or thrombocytopenia, or other grade 3 or 4.Toxicity judged to be related to lenalidomide do not dose below 5 mg every other day or 2.5 mg once daily.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

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 SmPC 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 and 5.3). 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 1 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 or shortly after he has stopped taking Lenalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use at least 1 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 healthcare 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 2 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, MDS and MCL taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see section 4.5). If a patient is currently using combined oral contraception the patient should switch to 1 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, semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of lenalidomide.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 6.6).

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 healthcare professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before treatment is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform the patient 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 as agreed with each National Competent Authority. In collaboration with each National Competent Authority, a controlled access programme has been implemented which includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collection of information relating to the indication in order to monitor 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 according to the approved indications dosing regimens (see section 4.2), 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 (e.g. 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, MDS and MCL, 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 MCL patients, the monitoring scheme should be every 2 weeks in cycles 3 and 4, and then at the start of each cycle. In FL, the monitoring scheme should be weekly for the first 3 weeks of cycle 1 (28 days), every 2 weeks during cycles 2 through 4, and then at the start of each cycle thereafter. A dose interruption and/or 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 epistaxis, 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.

- NDMM: 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).

- NDMM: 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%).

- NDMM: 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 4 - 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).

- NDMM: 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 NDMM 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 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 1 prior therapy

The combination of lenalidomide with dexamethasone in multiple myeloma patients with at least 1 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 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).

- MDS

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

- MCL

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

- FL

The combination of lenalidomide with rituximab in FL patients is associated with a higher incidence of grade 3 or 4 neutropenia compared with patients on the placebo/rituximab arm. Febrile neutropenia and grade 3 or 4 thrombocytopenia 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 NDMM.

The combination of lenalidomide with IV 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. Cases of TLS and tumour flare reaction (TFR), including fatal cases, have been reported (see section 4.8). 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.

- MCL

Careful monitoring and evaluation for TFR is recommended. Patients with high MCL international prognostic index (MIPI) at diagnosis or bulky disease (at least 1 lesion that is $\geq$ 7 cm in the longest diameter) at baseline may be at risk of TFR. TFR 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).

- FL

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 the individual patient (see sections 4.2 and 4.8).

Careful monitoring and evaluation for TLS is recommended. Patients should be well hydrated and receive TLS prophylaxis, in addition to weekly chemistry panels during the first cycle or longer, as clinically indicated (see sections 4.2 and 4.8).

Tumour burden

- MCL

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 TFR. Please refer to section 4.2 for dose adjustments for TFR. High tumour burden was defined as at least 1 lesion ≥ 5 cm in diameter or 3 lesions ≥ 3 cm

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 in patients treated with lenalidomide (see section 4.8). Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Lenalidomide must be discontinued for angioedema, anaphylactic reaction, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second primary malignancies

An increase of second primary malignancies (SPM) has been 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 NDMM patients not eligible for transplant, a 4.9 - fold increase in incidence rate of haematologic SPM (cases of acute myeloid leukaemia (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 haematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide in combination with dexamethasone until progression

or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In NDMM patients receiving lenalidomide in combination with bortezomib and dexamethasone, the haematologic SPM incidence rate was 0.00 - 0.16 per 100 person-years and the incidence rate of solid tumour SPM was 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 (SCT). Though this risk is not yet fully characterized, it should be kept in mind when considering and using lenalidomide in this setting.

The incidence rate of haematologic 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 haematologic SPM must be taken into account before initiating treatment with lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Progression to AML 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 2 clinical trials of lenalidomide in low- or intermediate-1-risk MDS, 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 1 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 – 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to AML. In a post-hoc analysis of a clinical trial of lenalidomide in low- or intermediate-1-risk MDS (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 MCL

In MCL, AML, B-cell malignancies and non-melanoma skin cancer (NMSC) are identified risks.

Second primary malignancies in FL

In a relapsed/refractory iNHL study which included FL patients, no increased risk of SPMs in the lenalidomide/rituximab arm, compared to the placebo/rituximab arm, was observed. Haematologic SPM of AML occurred in 0.29 per 100 person-years in the lenalidomide/rituximab arm compared with 0.29 per 100 person-years in patients receiving placebo/rituximab. The incidence rate of haematologic plus solid tumour SPMs (excluding non-melanoma skin cancers) was 0.87 per 100 person-years in the lenalidomide/rituximab arm, compared to 1.17 per 100 person-years in patients receiving placebo/rituximab with a median follow-up of 30.59 months (range 0.6-50.9 months).

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

Physicians should monitor patients for the development of SPMs. Both the potential benefit of lenalidomide and the risk of 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 (e.g. 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 HBV. Some of these cases have progressed to acute hepatic failure resulting in discontinuation of lenalidomide and adequate antiviral treatment. HBV 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 $\geq$ 2 or Cl_{Cr} < 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 $\geq$ 2 or Cl_{Cr} < 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.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

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% confidence interval(CI): 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 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 malformation in monkeys similar to those described with thalidomide (see section 5.3). 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 - 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
NDMM: 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:

- Pneumonia (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 anaemia (21.0% [13.8%]).

NDMM: 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 IV 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%).

NDMM: 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%).

NDMM: patients who are not eligible for transplant treated with lenalidomide in combination with melphalan 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%), anaemia (5.3%).

The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were:

- Neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leucopenia (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 1 prior therapy

In 2 phase III 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%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

MDS

The overall safety profile of lenalidomide in patients with MDS is based on data from a total of 286 patients from 1 phase II study and 1 phase III study (see section 5.1). In the phase II, all 148 patients were on lenalidomide treatment. In the phase III 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 III 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%).

MCL

The overall safety profile of lenalidomide in patients with MCL is based on data from 254 patients from a phase II 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%), anaemia (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 1 lesion ≥ 5 cm in diameter or 3 lesions

≥ 3 cm.

FL

The overall safety profile of lenalidomide in combination with rituximab in patients with previously treated FL is based on data from 294 patients from a phase III randomised, controlled study NHL-007. Additionally, adverse drug reactions from supportive study NHL-008 have been included in table 5.

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 with the 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 multiple myeloma

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 vs. 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[1,2] Upper respiratory tract infection Neutropenic infection Bronchitis[1] Influenza[1] Gastroenteritis[1] Sinusitis	Very common Pneumonias[1,2] Neutropenic infection Common Sepsis[1,4] Bacteraemia Lung infection[1] Lower respiratory tract

	Nasopharyngitis Rhinitis <u>Common</u> Infection[1] Urinary tract infection[1,3] Lower respiratory tract infection Lung infection[1]	infection bacterial Bronchitis[1] Influenza[1] Gastroenteritis[1] Herpes zoster[1] Infection[1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	<u>Common</u> MDS[1,3]	
Blood and lymphatic system disorders	<u>Very common</u> Neutropenia[1,5] Febrile neutropenia[1,5] Thrombocytopenia[1,5] Anaemia Leucopoenia[1] Lymphopenia	<u>Very common</u> Neutropenia[1,5] Febrile neutropenia[1,5] Thrombocytopenia[1,5] Anaemia Leucopoenia[1] Lymphopenia <u>Common</u> Pancytopenia[1]
Metabolism and nutrition disorders	<u>Very common</u> Hypokalaemia	<u>Common</u> Hypokalaemia Dehydration
Nervous system disorders	<u>Very common</u> Paraesthesia <u>Common</u> Peripheral neuropathy[6]	<u>Common</u> Headache
Vascular disorders	<u>Common</u> Pulmonary embolism[1,3]	<u>Common</u> Deep vein thrombosis[1,5,7]
Respiratory, thoracic and mediastinal disorders	<u>Very common</u> Cough <u>Common</u> Dyspnoea[1] Rhinorrhoea	<u>Common</u> Dyspnoea[1]
Gastrointestinal disorders	<u>Very common</u> Diarrhoea Constipation Abdominal pain Nausea <u>Common</u> Vomiting, Abdominal pain upper	<u>Common</u> Diarrhoea Vomiting Nausea
Hepatobiliary disorders	<u>Very common</u> Abnormal liver function tests	<u>Common</u> Abnormal liver function tests
Skin and subcutaneous tissue disorders	<u>Very common</u> Rash, Dry skin	<u>Common</u> 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

[1] Adverse reactions reported as serious in clinical trials in patients with NDMM who had undergone ASCT.
[2] "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.
[3] Applies to serious adverse drug reactions only.
[4] "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis.
[5] See section 4.8 description of selected adverse reactions.
[6] "Peripheral neuropathy" combined AE term includes the following preferred terms (PTs): Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy.
[7] "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis.

Tabulated summary for combination therapy in multiple myeloma
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 vs. 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[1,2] Upper respiratory tract infection[1] Bacterial, viral and fungal infections (including opportunistic infections)[1] Nasopharyngitis Pharyngitis Bronchitis[1] Rhinitis Common Sepsis[1,2] Lung infection[2] Urinary tract infection[2]	Common Pneumonia[1,2] Bacterial, viral and fungal infections (including opportunistic infections)[1] Cellulitis[1] Sepsis[1,2] Lung infection[2] Bronchitis[1] Respiratory tract infection[2] Urinary tract infection[2] Enterocolitis infectious

	Sinusitis[1]	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma[1,3] Squamous skin cancer[1,3,4]	Common AML[1] MDS[1] Squamous cell carcinoma of skin[1,3,5] Uncommon T-cell type acute leukaemia[1] Basal cell carcinoma[1,3] TLS
Blood and lymphatic system disorders	Very common Neutropenia[1,2,3] Thrombocytopenia[1,2,3] Anaemia[1] Haemorrhagic disorder[3] Leucopenia Lymphopenia Common Febrile neutropenia[1,3] Pancytopenia[1] Uncommon Haemolysis Autoimmune haemolytic anaemia Haemolytic anaemia	Very common Neutropenia[1,2,3] Thrombocytopenia[1,2,3] Anaemia[1] Leucopenia Lymphopenia Common Febrile neutropenia[1,3] Pancytopenia[1] Haemolytic anaemia Uncommon Hypercoagulation Coagulopathy
Immune system disorders	Uncommon Hypersensitivity[3]	
Endocrine disorders	Common Hypothyroidism	
Metabolism and nutrition disorders	Very common Hypokalaemia[1,2] Hyperglycaemia Hypoglycaemia Hypocalcaemia[1] Hyponatraemia[1] Dehydration[2] Decreased appetite[2] Weight decreased Common Hypomagnesaemia Hyperuricaemia Hypercalcaemia[6]	Common Hypokalaemia[1,2] Hyperglycaemia Hypocalcaemia[1] Diabetes mellitus[1] Hypophosphatemia Hyponatraemia[1] Hyperuricaemia Gout Dehydration[2] Decreased appetite[2] Weight decreased
Psychiatric disorders	Very common Depression Insomnia Uncommon Loss of libido	Common Depression Insomnia
Nervous system disorders	Very common Peripheral neuropathies[2]	Very common Peripheral neuropathies[2]

	Paraesthesia Dizziness[2] Tremor Dysgeusia Headache <u>Common</u> Ataxia Balance impaired Syncope[2] Neuralgia Dysaesthesia	 <u>Common</u> Cerebrovascular accident[1] Dizziness[2] Syncope[2] Neuralgia <u>Uncommon</u> Intracranial haemorrhage[3] Transient ischaemic attack Cerebral ischemia
Eye disorders	<u>Very common</u> Cataracts Blurred vision <u>Common</u> Reduced visual acuity	<u>Common</u> Cataract <u>Uncommon</u> Blindness
Ear and labyrinth disorders	<u>Common</u> Deafness (including hypoacusis) Tinnitus	
Cardiac disorders	<u>Common</u> Atrial fibrillation[1,2] Bradycardia <u>Uncommon</u> Arrhythmia QT prolongation Atrial flutter Ventricular extrasystoles	<u>Common</u> Myocardial infarction (including acute)[1,3] Atrial fibrillation[1,2] Congestive cardiac failure[1] Tachycardia Cardiac failure[1,2] Myocardial ischemia[1]
Vascular disorders	<u>Very common</u> Venous thromboembolic events[3] predominantly deep vein thrombosis and pulmonary embolism[1,2,3] Hypotension[2] <u>Common</u> Hypertension Ecchymosis[3]	<u>Very common</u> Venous thromboembolic events[3] predominantly deep vein thrombosis and pulmonary embolism[1,2,3] <u>Common</u> Vasculitis Hypotension[2] Hypertension <u>Uncommon</u> Ischemia Peripheral ischemia Intracranial venous sinus thrombosis
Respiratory, thoracic and mediastinal disorders	<u>Very common</u> Dyspnoea[1,2] Epistaxis[3] Cough	<u>Common</u> Respiratory distress[1] Dyspnoea[1,2] Pleuritic pain[2]

	<u>Common</u> Dysphonia Rhinorrhoea	Hypoxia[2]
Gastrointestinal disorders	<u>Very common</u> Diarrhoea[1,2] Constipation[1] Abdominal pain[2] Nausea Vomiting[2] Dyspepsia Dry mouth Stomatitis <u>Common</u> Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)[2,3] Dysphagia <u>Uncommon</u> Colitis Caecitis	<u>Common</u> Gastrointestinal haemorrhage[1,2,3] Small intestinal obstruction[2] Diarrhoea[2] Constipation[1] Abdominal pain[2] Nausea Vomiting[2]
Hepatobiliary disorders	<u>Very common</u> Alanine aminotransferase increased Aspartate aminotransferase increased <u>Common</u> Hepatocellular injury[2] Abnormal liver function tests[1] Hyperbilirubinaemia <u>Uncommon</u> Hepatic failure[3]	<u>Common</u> Cholestasis[1] Hepatotoxicity Hepatocellular injury[2] Alanine aminotransferase increased Abnormal liver function tests[1] <u>Uncommon</u> Hepatic failure[3]
Skin and subcutaneous tissue disorders	<u>Very common</u> Rashes[2] Pruritus <u>Common</u> Urticaria Hyperhidrosis Dry skin Skin hyperpigmentation Eczema Erythema <u>Uncommon</u> DRESS[2]	<u>Common</u> Rashes[2] <u>Uncommon</u> DRESS[2]

	Skin discolouration Photosensitivity reaction	
Musculoskeletal and connective tissue disorders	<u>Very common</u> Muscular weakness[2] Muscle spasm Bone pain[1] Musculoskeletal and connective tissue pain and discomfort (including back pain[1,2]) Pain in extremity Myalgia Arthralgia[1] <u>Common</u> Joint swelling	<u>Common</u> Muscular weakness[2] Bone pain[1] Musculoskeletal and connective tissue pain and discomfort (including back pain[1,2]) <u>Uncommon</u> Joint swelling
Renal and urinary disorders	<u>Very common</u> Renal failure (including acute)[1,2] <u>Common</u> Haematuria[3] Urinary retention Urinary incontinence <u>Uncommon</u> Acquired Fanconi syndrome	<u>Uncommon</u> Renal tubular necrosis
Reproductive system and breast disorders	<u>Common</u> Erectile dysfunction	
General disorders and administration site conditions	<u>Very common</u> Fatigue[1,2] Oedema (including peripheral oedema) Pyrexia[1,2] Asthenia Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) <u>Common</u> Chest pain[1,2] Lethargy	<u>Very common</u> Fatigue[1,2] <u>Common</u> Oedema peripheral Pyrexia[1,2] Asthenia
Investigations	<u>Very common</u> Blood alkaline phosphatase increased <u>Common</u> C-reactive protein increased	
Injury, poisoning and	<u>Common</u>	

procedural complications	Fall Contusion[3]	

[1] 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.
[2]. Adverse reactions reported as serious in clinical trials in patients with NDMM who had received lenalidomide in combination with bortezomib and dexamethasone.
[3] See section 4.8 description of selected adverse reactions.
[4] Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls.
[5] Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls
[6] Applies to serious adverse drug reactions only.

Tabulated summary from monotherapy

The following tables are derived from data gathered during the main studies in monotherapy for MDS and MCL.

Table 3: ADRs reported in clinical trials in patients with MDS treated with lenalidomide[1]

System organ class /	**All ADRs / frequency**	**Grade 3 – 4 ADRs / frequency**
Infections and infestations	Very common Bacterial, viral and fungal infections (including opportunistic infections)[2]	Very common Pneumonia[2] Common Bacterial, viral and fungal infections (including opportunistic infections)[2] Bronchitis
Blood and lymphatic system disorders	Very common Thrombocytopenia[2,3] Neutropenia[2,3] Leucopenia, Anaemia[2]	Very common Thrombocytopenia[2,3] Neutropenia[2,3] Leucopenia, Anaemia[2] Common Febrile neutropenia[2,3]
Endocrine disorders	Very common Hypothyroidism	
Metabolism and nutrition disorders	Very common Decreased appetite Common Iron overload Weight decreased	Common Hyperglycaemia[2] Decreased appetite
Psychiatric disorders		Common Altered mood[2,4]

Nervous system disorders	Very common Dizziness Headache Common Paraesthesia	
Cardiac disorders		Common Acute myocardial infarction[2,3] Atrial fibrillation[2] Cardiac failure[2]
Vascular disorders	Common Hypertension Haematoma	Common Venous thromboembolic events predominantly deep vein thrombosis and pulmonary embolism[2,3]
Respiratory, thoracic and mediastinal disorders	Very common Epistaxis[3]	
Gastrointestinal disorders	Very common Diarrhoea[2] Abdominal pain (including upper) Nausea Vomiting Constipation Common Dry mouth Dyspepsia	Common Diarrhoea[2] Nausea Toothache
Hepatobiliary disorders	Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and subcutaneous tissue disorders	Very common Rashes Dry skin Pruritus	Common Rashes Pruritus
Musculoskeletal and connective tissue disorders	Very common Muscle spasms Musculoskeletal pain (including back pain[2] and pain in extremity) Arthralgia Myalgia	Common Back pain[2]
Renal and urinary disorders		Common Renal failure[2]

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		Common Fall

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

[1] Algorithm applied for MDS:

- MDS phase III study (double-blind safety population, difference between lenalidomide 5/10 mg and placebo by initial dosing regimen occurring in at least 2 subjects):
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide and at least 2% difference in proportion between lenalidomide and placebo.
  - All treatment-emergent grade 3 or 4 adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo.
  - All treatment-emergent serious adverse events in 1% of subjects in lenalidomide and at least 1% difference in proportion between lenalidomide and placebo.
- MDS phase II study:
  - All treatment-emergent adverse events with ≥ 5% of lenalidomide treated subjects.
  - All treatment-emergent grade 3 or 4 adverse/events in 1% of lenalidomide treated subjects.
  - All treatment-emergent serious adverse events in 1% of lenalidomide treated subjects.

[2] Adverse events reported as serious in MDS clinical trials.

[3] See section 4.8 description of selected adverse reactions

[4] Altered mood was reported as a common serious adverse event in the MDS phase III study; it was not reported as a grade 3 or 4 adverse event.

Table 4: ADRs reported in clinical trials in patients with MCL treated with lenalidomide

System organ class /	**All ADRs / frequency**	**Grade 3 – 4 ADRs / frequency**

Infections and infestations	Very common Bacterial, viral and fungal infections (including opportunistic infections)[1] Nasopharyngitis Pneumonia[1] Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections)[1] Pneumonia[1]
Neoplasms benign, malignant and	Common TFR	Common TFR Squamous skin cancer[1,2] Basal cell carcinoma[1,2]
Blood and lymphatic system disorders	Very common Thrombocytopenia[2] Neutropenia[1,2] Leucopenia[1] Anaemia[1] Common Febrile neutropenia[1,2]	Very common Thrombocytopenia[2] Neutropenia[1,2] Anaemia[1] Common Febrile neutropenia[1,2] Leucopenia[1]
Metabolism and nutrition disorders	Very common Decreased appetite Weight decreased Hypokalaemia Common Dehydration[1]	Common Dehydration[1] Hyponatraemia Hypocalcaemia
Psychiatric disorders	Common Insomnia	
Nervous system disorders	Common Dysgeusia Headache Neuropathy peripheral	Common Peripheral sensory neuropathy Lethargy
Ear and labyrinth	Common Vertigo	
Cardiac disorders		Common Myocardial infarction (including acute)[1,2] Cardiac failure
Vascular disorders	Common Hypotension[1]	Common Deep vein thrombosis[1] Pulmonary embolism[1,2] Hypotension[1]
Respiratory, thoracic	Very common Dyspnoea[1]	Common Dyspnoea[1]

Gastrointestinal disorders	Very common Diarrhoea[1] Nausea[1] Vomiting[1] Constipation Common Abdominal pain[1]	Common Diarrhoea[1] Abdominal pain[1] 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[1]	Common Back pain Muscular weakness[1] Arthralgia Pain in extremity
Renal and urinary		Common Renal failure[1]
General disorders and administration site conditions	Very common Fatigue Asthenia[1] Peripheral oedema Influenza like illness syndrome (including pyrexia[1], cough) Common Chills	Common Pyrexia[1] Asthenia[1] Fatigue

Algorithm applied for MCL:

- MCL controlled phase II study:
  - All treatment-emergent adverse events with ≥ 5% of subjects in lenalidomide arm and at least 2% difference in proportion between lenalidomide and control arm.
  - All treatment-emergent grade 3 or 4 adverse events in ≥ 1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm.
  - All serious treatment-emergent adverse events in ≥ 1% of subjects in lenalidomide arm and at least 1.0% difference in proportion between lenalidomide and control arm.
- MCL single arm phase II study:
  - All treatment-emergent adverse events with ≥ 5% of subjects.
  - All grade 3 or 4 treatment-emergent adverse events reported in 2 or more subjects.
  - All serious treatment-emergent adverse events reported in 2 or more subjects.

[1] Adverse events reported as serious in MCL clinical trials.

[2] See section 4.8 description of selected adverse reactions.

Tabulated summary for combination therapy in FL
The following table is derived from data gathered during the main studies (NHL-007 and NHL-008) using lenalidomide in combination with rituximab for patients with FL.

Table 5: ADRs reported in clinical trials in patients with FL treated with lenalidomide in combination 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[1] Influenza Bronchitis Sinusitis Urinary tract infection	Common Pneumonia[1] Sepsis[1] Lung infection Bronchitis Gastroenteritis Sinusitis Urinary tract infection Cellulitis[1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Very common Tumour flare[2] Common Squamous cell carcinoma of skin[1,2,3]	Common Basal cell carcinoma[1,2]
Blood and lymphatic system disorders	Very common Neutropenia[1,2] Anaemia[1] Thrombocytopenia[2] Leucopenia[4] Lymphopenia[5]	Very common Neutropenia[1,2] Common Anaemia[1] Thrombocytopenia[2] Febrile neutropenia[1] Pancytopenia Leucopenia[4] Lymphopenia[5]
Metabolism and nutrition disorders	Very common Decreased appetite Hypokalaemia Common Hypophosphataemia Dehydration	Common Dehydration Hypercalcaemia[1] Hypokalaemia Hypophosphataemia Hyperuricaemia
Psychiatric disorders	Common Depression Insomnia	
Nervous system disorders	Very common Headache Dizziness Common Peripheral sensory neuropathy	Common Syncope

	Dysgeusia	
Cardiac disorders	Uncommon Arrhythmia[1]	
Vascular disorders	Common Hypotension	Common Pulmonary embolism[1,2] Hypotension
Respiratory, thoracic and mediastinal disorders	Very common Dyspnoea[1] Cough Common Oropharyngeal pain Dysphonia	Common Dyspnoea[1]
Gastrointestinal disorders	Very common Abdominal pain[1] Diarrhoea Constipation Nausea Vomiting Dyspepsia Common Upper abdominal pain Stomatitis Dry mouth	Common Abdominal pain[1] Diarrhoea Constipation Stomatitis
Skin and subcutaneous tissue disorders	Very common Rash[6] Pruritus Common Dry skin Night sweats Erythema	Common Rash[6] 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[1]
General disorders and administration site conditions	Very common Pyrexia Fatigue Asthenia Peripheral oedema Common Malaise	Common Fatigue Asthenia

	Chills	
Investigations	Very common Alanine aminotransferase increased Common Weight decreased Blood bilirubin increased	

Algorithm applied for FL:

- Controlled – phase III trial:
- NHL-007 ADRs – all treatment-emergent AEs with ≥ 5.0% of subjects in lenalidomide/rituximab arm and at least 2.0% higher frequency (%) in lenalidomide arm compared to control arm – (safety population).
- NHL-007 grade 3 – 4 ADRs – all grades 3 or grade 4 treatment-emergent AEs with at least 1.0% subjects in lenalidomide/rituximab arm and at least 1.0% higher frequency in lenalidomide arm compared to control arm – (safety population).
- NHL-007 serious ADRs – all serious treatment-emergent AEs with at least 1.0% subjects in lenalidomide/rituximab arm and at least 1.0% higher frequency in lenalidomide/rituximab arm compared to control arm – (safety population).

FL single arm – phase III trial:

- NHL-008 ADRs – all treatment-emergent adverse events with ≥ 5.0% of subjects.
- NHL-008 grade 3 – /4 ADRs – all grade 3 – 4 treatment-emergent adverse events reported in ≥ 1.0% of subjects.
- NHL-008 serious ADRs – all serious treatment-emergent adverse events reported in ≥ 1.0% of subjects.

[1] Adverse events reported as serious in FL clinical trials.
[2] See section 4.8 description of selected adverse reactions.
[3] Applies to serious adverse drug reactions only.
[4] Leucopenia includes PT leucopenia and white blood cell count decreased.
[5] Lymphopenia includes PT lymphopenia and lymphocyte count decreased.
[6] Rash includes PT of rash and rash maculo-papular.

Tabulated summary of post-marketing adverse reactions

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

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

System organ class / preferred term	**All ADRs / frequency**	**Grade 3-4 ADRs / frequency**
Infections and infestations	Not known Viral infections, including herpes zoster and HBV reactivation	Not known Viral infections, including herpes zoster and HBV reactivation
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Rare TLS
Blood and lymphatic system disorders	Not known Acquired haemophilia	

Immune system disorders	Rare Anaphylactic reaction[1] Not known Solid organ transplant rejection	Rare Anaphylactic reaction[1]
Endocrine disorders	Common Hyperthyroidism	
Respiratory, thoracic and mediastinal disorders	Uncommon Pulmonary hypertension	Rare Pulmonary hypertension Not known Interstitial pneumonitis
Gastrointestinal disorders		Not known Pancreatitis Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)[1]
Hepatobiliary disorders	Not known Acute hepatic failure[1] Hepatitis toxic[1] Cytolytic hepatitis[1] Cholestatic hepatitis[1] Mixed cytolytic/cholestatic hepatitis[1]	Not known Acute hepatic failure[1] Hepatitis toxic[1]
Skin and subcutaneous tissue disorders		Uncommon Angioedema Rare SJS[1] TEN[1] Not known Leukocytoclastic vasculitis DRESS[1]

[1]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. In monkeys lenalidomide induced malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

- NDMM: 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).

- NDMM: 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%).

- NDMM: Patients who are not eligible for transplant treated with lenalidomide in combination with dexamethasone

The combination of lenalidomide with dexamethasone in NDMM 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 NDMM patients is associated with a lower frequency of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18)compared with MPT (11.1%).

- NDMM: 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 NDMM 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 NDMM patients is associated with a higher frequency of grade 3 and 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

- Multiple myeloma: patients with at least 1 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 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).

- MDS patients

In MDS 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 III 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 III study).

- MCL patients

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

- FL patients

The combination of lenalidomide with rituximab in FL is associated with a higher rate of grade 3 or grade 4 neutropenia (50.7% in lenalidomide/rituximab treated patients compared with 12.2% in placebo/rituximab treated patients). All grade 3 or 4 neutropenia were reversible through dose interruption, reduction and/or supportive care with growth factors. Additionally, febrile neutropenia was observed infrequently (2.7% in lenalidomide/rituximab treated patients compared with 0.7% in placebo/rituximab treated patients).

Lenalidomide in combination with rituximab is also associated with a higher incidence of grade 3 or 4 thrombocytopenia (1.4% in lenalidomide/rituximab treated patients compared to 0% in placebo/rituximab patients).

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, MDS and MCL 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 and thalidomide has been reported in the literature. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section 4.4).

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

AML
- Multiple myeloma

Cases of AML have been observed in clinical trials of NDMM 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 NDMM in patients taking lenalidomide in combination with dexamethasone compared to thalidomide in combination with melphalan and prednisone.

- MDS

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 1 additional cytogenetic abnormality and 38.6% in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of lenalidomide in MDS, 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).

TFR and TLS
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 1 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 1 patient in each of the 2 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).

In study NHL-007, TFR was reported in 19/146 (13.0%) of patients in the lenalidomide/rituximab arm vs. 1/148 (0.7%) patients in the placebo/rituximab arm. Most TFRs (18 out of 19) reported in the lenalidomide/rituximab arm occurred during first 2 cycles of treatment. 1 FL patient in the lenalidomide/rituximab arm experienced a grade 3 TFR event vs. no patients in the placebo/rituximab arm. In study NHL-008, 7/177 (4.0%) of FL patients experienced TFR; (3 reports were grade 1 and 4 reports were grade 2 severity); while 1 report was considered serious. In study NHL-007, TLS occurred in 2 FL patients (1.4%) in the lenalidomide/rituximab arm and no FL patients in the placebo/rituximab arm; neither patient had a grade 3 or 4 event. TLS occurred in 1 FL patient (0.6%) in study NHL-008. This single event was identified as a serious, grade 3 adverse reaction. For study NHL-007 no patients had to discontinue lenalidomide/rituximab therapy due to TFR or TLS.

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

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

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 multiple myeloma plasma tumour cells, FL 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 tumour apoptosis in FL 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.

Clinical efficacy and safety

Lenalidomide efficacy and safety have been evaluated in 6 phase III studies in NDMM, 2 phase III studies in relapsed refractory multiple myeloma, 1 phase III study and 1 phase II study in MDS and 1 phase II study in MCL and 1 phase III and 1 phase IIIb study in iNHL as described below.

NDMM

- Lenalidomide maintenance in patients who have undergone ASCT

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

CALGB 100104
Patients between 18 and 70 years of age with active multiple myeloma requiring treatment and without prior progression after initial treatment were eligible.

Patients were randomised 1:1 within 90-100 days after ASCT to receive either lenalidomide or placebo maintenance. The maintenance dose was 10 mg once daily on days 1-28 of repeated 28-day cycles (increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity), and treatment was continued until disease progression.

The primary efficacy endpoint in the study was progression free survival (PFS) from randomisation to the date of progression or death, whichever occurred first; the study was not powered for the overall survival endpoint. In total 460 patients were randomised: 231 patients to lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

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

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

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

The results for the study, using a cut-off of 1 February 2016, are presented in table 7.

Table 7: Summary of overall efficacy data

	Lenalidomide (N = 231)	**Placebo (N = 229)**
Investigator-assessed PFS		
Median[1] PFS time, months (95% CI)[2]	**56.9** (41.9 - 71.7)	**29.4** (20.7 - 35.5)
HR (95% CI)[3]; p-value[4]	**0.61** (0.48 - 0.76); <0.001	
PFS2[5]		
Median[1] PFS2 time, months (95% CI)[2]	**80.2** (63.3 - 101.8)	**52.8** (41.3 - 64.0)
HR (95% CI)[3] ; p-value[4]	**0.61** (0.48 - 0.78); <0.001	
OS		
Median[1] OS time, months (95% CI)[2]	**111.0** (101.8 - NE)	**84.2** (71.0 - 102.7)
8-year survival rate, % (SE)	60.9 (3.78)	44.6 (3.98)
HR (95% CI)[3] ; p-value[4]	**0.61** (0.46, 0.81); <0.001	
Follow-up		
Median[6] (min - max), months: All surviving patients	**81.9** (0.0- 119.8)	**81.0** (4.1- 119.5)

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

standard error.
[1] The median is based on the Kaplan-Meier estimate.
[2] The 95% CI about the median.
[3] Based on Cox proportional hazards model comparing the hazard functions associated with the indicated treatment arms.
[4] The p-value is based on the unstratified log-rank test of Kaplan-Meier curve differences between the indicated treatment arms.
[5] Exploratory endpoint (PFS2). Lenalidomide received by subjects in the placebo arm who crossed over prior to PD upon study unblinding was not considered as a second-line therapy.
[6] Median follow-up post-ASCT for all surviving subjects.
Data cut-off dates: 17 Dec 2009 and 01 Feb 2016

IFM 2005-02
Patients aged < 65 years at diagnosis who had undergone ASCT and had achieved at least a stable disease response at the time of haematologic recovery were eligible. Patients were randomised 1:1 to receive either lenalidomide or placebo maintenance (10 mg once daily on days 1-28 of repeated 28-day cycles increased up to 15 mg once daily after 3 months in the absence of dose-limiting toxicity) following 2 courses of lenalidomide consolidation (25 mg/day, days 1-21 of a 28-day cycle). Treatment was to be continued until disease progression.

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

The study was unblinded upon the recommendations of the data monitoring committee after surpassing the threshold for a pre-planned interim analysis of PFS. After unblinding, patients receiving placebo were not crossed over to lenalidomide therapy prior to progressive disease. The lenalidomide arm was discontinued, as a proactive safety measure, after observing an imbalance of SPMs (see Section 4.4).

The results of PFS at unblinding, following a pre-planned interim analysis, using a cut-off of 07 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favouring lenalidomide (HR = 0.52; 95% CI: 0.41 - 0.66; p <0.001). The median overall PFS was 40.1 months (95% CI: 35.7-42.4) in the lenalidomide arm vs. 22.8 months (95% CI: 20.7-27.4) in the placebo arm.

The PFS benefit was less in the subgroup of patients with CR than in the subgroup of patients who had not achieved a CR.

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

- Lenalidomide in combination with bortezomib and dexamethasone in patients who are not eligible for SCT

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

Patients in the lenalidomide, bortezomib and dexamethasone (RVd) arm received lenalidomide 25 mg/day orally on days 1-14, IV bortezomib 1.3 mg/m2 on days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of repeated 21-day cycles for up to 8 21-day cycles (24 weeks). Patients in the lenalidomide and dexamethasone (Rd) arm received lenalidomide 25 mg/day orally on days 1-21, and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles for up to 6 28-day cycles (24 weeks). Patients in both arms took continued Rd: lenalidomide 25 mg/day orally on days 1-21 and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles. Treatment was to be continued until disease progression.

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

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

The results for the study, using a cut-off of 01 December 2016, where the median follow-up time for all surviving subjects was 69.0 months, are presented in table 8. The benefit favouring RVd was observed regardless of eligibility for SCT.

Table 8: Summary of overall efficacy data

	Initial treatment	
	RVd (3-week cycles × 8) (N = 263)	**Rd (4-week cycles × 6) (N = 260)**
IRAC-assessed PFS (months)		
Median[1] PFS time, months (95% CI)[2]	**41.7** (33.1-51.5)	**29.7** (24.2-37.8)
HR (95% CI)[3]; p-value[4]	**0.76** (0.62-0.94); 0.010	
OS (months)		
Median1 OS time, months (95% CI)[2]	**89.1** (76.1-NE)	**67.2** (58.4-90.8)
HR (95% CI)3; p-value[4]	**0.72** (0.56-0.94); 0.013	
Response -n (%)		
Overall response: CR, VGPR or PR	199 (75.7)	170 (65.4)
≥ VGPR	153 (58.2)	83 (31.9)
Follow-up (months)		
Median[5] (min-max): All patients	**61.6** (0.2-99.4)	**59.4** (0.4-99.1)

CI = confidence interval; HR = hazard ratio; IRAC = independent response adjudication committee; max = maximum; min = minimum; NE = not estimable; OS = overall survival; PFS = progression-free survival.

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

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

[3] Based on unstratified Cox proportional hazards model comparing hazard functions associated with treatment arms (RVd:Rd).
[4] The p-value is based on unstratified log-rank test.
[5] Median follow-up was calculated from the date of randomisation.
Data cut-off date: 01 Dec 2016.

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

- Lenalidomide in combination with dexamethasone in patients who are not eligible for SCT

The safety and efficacy of lenalidomide was assessed in a phase III, multicentre, randomised, open-label, 3-arm study (MM-020) of patients who were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for SCT because they declined to undergo SCT or SCT is not available to the patient due to cost or other reason. The study (MM-020) compared lenalidomide and dexamethasone (Rd) given for 2 different durations of time (i.e. until progressive disease [Arm Rd] or for up to 18 28-day cycles [72 weeks, Arm Rd18]) to melphalan, prednisone and thalidomide (MPT) for a maximum of 12 42-day cycles (72 weeks). Patients were randomised (1:1:1) to 1 of 3 treatment arms. Patients were stratified at randomisation by age (≤75 vs. >75 years), stage (ISS stages I and II vs. stage III), and country.

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

The primary efficacy endpoint in the study was progression free survival (PFS). In total 1,623 patients were enrolled into the study, with 535 patients randomised to Rd, 541 patients randomised to Rd18 and 547 patients randomised to MPT. The demographics and disease-related baseline characteristics of the patients were well balanced in all 3 arms. In general, study subjects had advanced-stage disease: Of the total study population, 41% had ISS stage III, 9% had severe renal insufficiency (creatinine clearance [Cl_{Cr}] < 30 mL/min). The median age was 73 in the 3 arms.

In an updated analysis of PFS, PFS2 and OS using a cut off of 03 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in table 9:

Table 9: Summary of overall efficacy data

	Rd (N = 535)	**Rd18 (N = 541)**	**MPT (N = 547)**
Investigator-assessed PFS - (months)			
Median[1] PFS time, months (95% CI)[2]	26.0 (20.7-29.7)	21.0 (19.7-22.4)	21.9 (19.8-23.9)
HR (95% CI)[3] p-value[4]			
Rd vs MPT	0.69 (0.59-0.80); <0.001		

Rd vs Rd18	0.71 (0.61-0.83); <0.001		
Rd18 vs MPT	0.99 (0.86-1.14); 0.866		
PFS2[5] - (months)			
Median[1] PFS2 time, months (95% CI)[2]	42.9 (38.1-47.4)	40.0 (36.2-44.2)	35.0 (30.4-37.8)
HR (95% CI)[3]; p-value[4]			
Rd vs MPT	0.74 (0.63-0.86); <0.001		
Rd vs Rd18	0.92 (0.78-1.08); 0.316		
Rd18 vs MPT	0.80 (0.69-0.93); 0.004		
OS (months)			
Median[1] OS time, months (95% CI)[2]	58.9 (56.0-NE)	56.7 (50.1-NE)	48.5 (44.20-52.0)
HR (95% CI)[3]; p-value[4]			
Rd vs MPT	0.75 (0.62-0.90); 0.002		
Rd vs Rd18	0.91 (0.75-1.09); 0.305		
Rd18 vs MPT	0.83 (0.69-0.99); 0.034		
Follow-up (months)			
Median[6] (min, max): All patients	40.8 (0.0-65.9)	40.1 (0.4-65.7)	38.7 (0.0-64.2)
Myeloma response[7] n (%)			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)
Duration of response - (months)[8]			
Median[1] (95% CI)[2]	35.0 (27.9-43.4)	22.1 (20.3-24.0)	22.3 (20.2-24.9)

CI = confidence interval; CR = complete response; d = low-dose dexamethasone; HR = hazard ratio; M = melphalan; max = maximum; min = minimum; NE = not estimable; OS = overall survival; P = prednisone; PFS = progression-free survival; PR = partial response; R = lenalidomide; Rd = Rd given until documentation of progressive disease; Rd18 = Rd given for 18 cycles; T = thalidomide; VGPR = very good partial response; vs = versus.

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

[2] The 95% CI about the median.

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

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

[5] Exploratory endpoint (PFS2).

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

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

[8] Data cut off date 24 May 2013.

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

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

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

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

In an analysis of PFS, PFS2, OS using a cut off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 10:

Table 10: Summary of overall efficacy data

	MPR+R (N = 152)	**MPR+p (N = 153)**	**MPp +p (N = 154)**
Investigator-assessed PFS (months)			
Median[1] PFS time, months (95 % CI)	27.4 (21.3- 35.0)	14.3 (13.2-15.7)	13.1 (12.0-14.8)
HR (95% CI); p-value			
MPR+R vs MPp+p	0.37 (0.27-0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35-0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60-1.01); 0.059		
PFS2- (months) [2]			
Median[1] PFS2 time, months (95% CI)	39.7 (29.2-48.4)	27.8 (23.1-33.1)	28.8 (24.3-33.8)
HR (95% CI); p-value			
MPR+R vs MPp+p	0.70 (0.54-0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59-1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71-1.19); 0.051		
OS (months)			
Median[1] OS time, months	55.9 (49.1-67.5)	51.9 (43.1-60.6)	53.9 (47.3-64.2)

(95% CI)			
HR (95% CI); p-value			
MPR+R vs MPp+p	0.95 (0.70-1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65-1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79-1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8-73.8)	46.3 (0.5-71.9)	50.4 (0.5-73.3)
Investigator-assessed myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)
(SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed duration of response (CR+PR) - (months)			
Median[1] (95% CI)	26.5 (19.4-35.8)	12.4 (11.2-13.9)	12.0 (9.4-14.5)

CI = confidence interval; CR = complete response; HR = Hazard ratio; M = melphalan;; OS = overall survival; p = placebo; P = prednisone;
PD = progressive disease; PR = partial response; R = lenalidomide; SD = stable disease; VGPR = very good partial response.
[1] The median is based on the Kaplan-Meier estimate
[2]PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomisation to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

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

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

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

Multiple myeloma with at least 1 prior therapy
The efficacy and safety of lenalidomide were evaluated in 2 phase III multi-centre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy vs. dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

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

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

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

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

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 11 summarises the results of the follow-up efficacy analyses - pooled studies MM-009 and MM-010.

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

Table 11: Summary of results of efficacy analyses as of cut-off date for extended follow-up -pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 02 March 2008, respectively)

Endpoint	len/dex (N = 353)	placebo/dex (N = 351)	
Time to event			**Hazard ratio (95% CI), p-value[1]**
Time to progression Median (95% CI), weeks	60.1 (44.3-73.1)	20.1 (17.7-20.3)	0.350 (0.287-0.426), p < 0.001
Progression free survival Median (95% CI), weeks	48.1 (36.4-62.1)	20.0 (16.1-20.1)	0.393 (0.326-0.473), p < 0.001
Overall survival Median (95% CI), weeks 1-year overall survival rate	164.3 (145.1-192.6) 82%	136.4 (113.1-161.7) 75%	0.833 (0.687-1.009), p = 0.045
Response rate			**Odds ratio (95% CI), p-value[2]**
Overall response n, (%)	212 (60.1)	75 (21.4)	5.53 (3.97-7.71), p < 0.001
Complete response n, (%)	58 (16.4)	11 (3.1)	6.08 (3.13-11.80), p < 0.001

[1] Two-tailed log rank test comparing survival curves between treatment groups.
[2] Two-tailed continuity-corrected chi-square test.

MDS

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

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

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

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

Table 12: Summary of efficacy results – studies MDS-004 (double-blind phase) and MDS-003, intent-to-treat population endpoint

	MDS-004 N = 205			MDS-003 N = 148
	10 mg[1] N = 69	**5 mg[2] N = 69**	**Placebo[3] N = 67**	**10 mg N = 148**
Transfusion independence (≥ 182 days)[4]	38 (55.1%)	24 (34.8%)	4 (6.0%)	86 (58.1%)
Transfusion independence (≥ 56 days)[4]	42 (60.9%)	33 (47.8%)	5 (7.5%)	97 (65.5%)
Median time to transfusion independence (weeks)	4.6	4.1	0.3	4.1
Median duration of transfusion independence (weeks)	NR[5]	NR	NR	114.4
Median increase in Hgb, g/dL	6.4	5.3	2.6	5.6

[1] Subjects treated with lenalidomide 10 mg on 21 days of 28-day cycles.
[2] Subjects treated with lenalidomide 5 mg on 28 days of 28-day cycles.
[3] The majority of patients on placebo discontinued the double-blind treatment for lack of efficacy after 16 weeks of treatment before entering the open-label phase.
[4] Associated with an increase in Hgb of ≥ 1g/dL.
[5] Not reached (i.e. the median was not reached).

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

The median time to transfusion independence in the lenalidomide 10 mg arm was 4.6 weeks. The median duration of transfusion independence was not reached in any of the treatment arms but should exceed 2 years for the lenalidomide-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

Additional endpoints of the study included cytogenetic response (in the 10 mg arm major and minor cytogenetic responses were observed in 30.0% and 24.0% of subjects, respectively), assessment of health related quality of life (HRQoL) and progression to AML. Results of the cytogenetic response and HRQoL were consistent with the findings of the primary endpoint and in favour of lenalidomide treatment compared to placebo.

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

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

MCL

The efficacy and safety of lenalidomide were evaluated in patients with MCL in a phase II, multicentre, randomised open-label study vs. single agent of investigator's choice in patients who were refractory to their last regimen or had relapsed 1 3 times (study MCL-002).

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

Lenalidomide was administered orally 25 mg once daily for the first 21 days (day 1 – 21) of repeating 28-day cycles until progression or unacceptable toxicity. Patients with moderate renal insufficiency were to receive a lower starting dose of lenalidomide 10 mg daily on the same schedule.

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

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

The efficacy results for the intent-to-treat (ITT) population were assessed by the independent review committee (IRC), and are presented in Table 13 below.

Table 13: Summary of efficacy results – study MCL-002, ITT population

	Lenalidomide arm N = 170	**Control arm N = 84**
PFS		
PFS, median[1] [95% CI][2] (weeks)	37.6 [24.0 – 52.6]	22.7 [15.9 – 30.1]
Sequential HR [95% CI][5]	0.61 [0.44 – 0.84]	
Sequential log-rank test, p-value[5]	0.004	
Response[1], n (%)		
CR	8 (4.7)	0 (0.0)
PR	60 (35.3)	9 (10.7)
SD[2]	50 (29.4)	44 (52.4)
PD	34 (20.0)	26 (31.0)
Not done / missing	18 (10.6)	5 (6.0)
ORR (CR, CRu, PR), n (%) [95% CI][3]	68 (40.0) [32.58 – 47.78]	9 (10.7)[4] [5.02 – 19.37]
p-value[5]	< 0.001	
CRR (CR, CRu), n (%) [95% CI][3]	8 (4.7) [2.05 – 9.06]	0 (0.0) [95.70 – 100.00]
p-value[5]	0.043	
Duration of response, median[1] [95% CI] (weeks)	69.6 [41.1 – 86.7]	45.1 [36.3 – 80.9]

OS	
HR [95% CI][3]	0.89 [0.62 – 1.28]
Log-rank test, p-value	0.520

CI = confidence interval; CR = complete response; CRR = complete response rate; CRu = complete response unconfirmed; DMC = data monitoring committee; ITT = intent-to-treat; HR = hazard ratio; KM = Kaplan-Meier; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR= partial response; SD = stable disease.

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

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

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

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

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

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

FL

AUGMENT - CC-5013-NHL-007

The efficacy and safety of lenalidomide in combination with rituximab vs. rituximab plus placebo was evaluated in patients with relapsed/refractory iNHL including FL in a phase 3, multicentre, randomised, double- blind controlled study (CC-5013-NHL-007 [AUGMENT]).

A total of 358 patients who were at least 18 years of age with histologically confirmed MZL or grade 1, 2 or 3a FL (CD20+ by flow cytometry or histochemistry) as assessed by the investigator or local pathologist were randomised in a 1:1 ratio. Subjects had been previously treated with at least 1 prior systemic chemotherapy, immunotherapy or chemoimmunotherapy.

Lenalidomide was administered orally 20 mg once daily for the first 21 days of repeating 28-day cycles for 12 cycles or until unacceptable toxicity. The dose of rituximab was 375 mg/m2 every week in cycle 1 (days 1, 8, 15, and 22) and on day 1 of every 28-day cycle from cycles 2 through 5. All dosage calculations for rituximab were based on the patient's body surface area (BSA), using actual patient weight.

The demographic and disease-related baseline characteristics were similar across the 2 treatment groups.

The primary objective of the study was to compare the efficacy of lenalidomide in combination with rituximab to rituximab plus placebo in subjects with relapsed/refractory FL grade 1, 2 or 3a or MZL. Efficacy determination was based upon PFS as the primary endpoint, as assessed by the IRC using the 2007 International Working Group (IWG) criteria but without positron emission tomography (PET).

The secondary objectives of the study were to compare the safety of lenalidomide in combination with rituximab vs. rituximab plus placebo. Further secondary objectives were to compare the efficacy of rituximab plus lenalidomide vs. rituximab plus placebo using the following other parameters of efficacy: Overall response rate (ORR), CR rate, and duration of response (DoR) by IWG 2007 without PET and OS.

Results from the overall population including FL and MZL showed that at a median follow-up of 28.3°months, the study met its primary endpoint of PFS with a hazard ratio (HR) (95% CI of 0.45 (0.33 – 0.61) p-value < 0.0001. The efficacy results from the follicular lymphoma population are presented in table 14.

Table 14: Summary of FL efficacy data – Study CC-5013-NHL-007

	FL (N = 295)	
	Lenalidomide and rituximab (N = 147)	**Placebo and rituximab (N = 148)**
PFS (EMA censoring rules)		
Median PFS1 (95% CI) (months)	39.4 (25.1-NE)	13.8 (11.2-16.0)
HR (95% CI)	0.40 (0.29-0.55)[2]	
p-value	< 0.0001[3]	
Objective response[4] (CR +PR), n (%) (IRC, 2007 IWGRC) 95% CI[6]	118 (80.3) (72.9-86.4)	82 (55.4) (47.0-63.6)
Complete response[4], n (%) (IRC, 2007 IWGRC) 95% CI[6]	51 (34.7) (27.0-43.0)	29 (19.6) (13.5-26.9)
Duration of response[4] (median) (months) 95% CI[1]	36.6 (24.9-NE)	15.5 (11.2-25.0)
OS[4,5]		
OS rate at 5 years, n (%) 95% CI	126 (85.9) (78.6- 90.9)	114 (77.0) (68.9-83.3)
HR (95% CI)	0.45 (0.22-0.92)[2]	
Follow-up		
Median duration of follow-up (min, max) (months)	67.81 (0.5,89.3)	65.72 (0.6,90.9)

CI = confidence interval; CR = complete response; HR = hazard ratio; IRC = independent review committee; IWGRC = international working group response criteria; OS = overall survival; PFS = progression-free survival; PR= partial response.

[1] Median estimate from Kaplan-Meier analysis.

[2] Hazard ratio and its confidence interval were estimated from unstratified Cox proportional hazard model.

[3] P-value from log-rank test.

[4] Secondary and exploratory endpoints are not α-controlled.

[5] With a median follow-up of 66.14 months, there were 19 deaths in the R2 arm and

38 deaths in the control arm.
[6] Exact confidence interval for binomial distribution.

FL for patients refractory to rituximab
MAGNIFY - CC-5013-NHL-008
A total of 232 subjects who were at least 18 years of age with histologically confirmed FL (grade 1, 2, 3a or MZL), as assessed by the investigator or local pathologist, were enrolled into the initial treatment period with 12 cycles of lenalidomide plus rituximab. Subjects who achieved CR/CRu, PR, or SD by the end of the induction treatment period were randomised to enter the maintenance treatment period. All enrolled subjects must have previously been treated with at least 1 prior systemic antilymphoma therapy. In contrast to study NHL-007, the NHL-008 study included patients who were refractory to rituximab (no response or relapsed within 6 months of rituximab treatment or who were double-refractory to rituximab and chemotherapy).

During the induction treatment period, lenalidomide 20 mg was given on days 1-21 of repeated 28-day cycles for up to 12 cycles or until unacceptable toxicity, or withdrawal of consent or disease progression. The dose of rituximab was 375 mg/m2 every week in cycle 1 (days 1, 8, 15, and 22) and on day 1 of every other 28-day cycle (cycles 3, 5, 7, 9, and 11) up to 12 cycles therapy. All dosage calculations for rituximab were based on the patient body surface area (BSA) and actual weight.

The data presented are based on an interim analysis focusing on the single-arm induction treatment period. Efficacy determinations are based on ORR by best response as the primary endpoint, using a modification of the 1999 international working group response criteria (IWGRC). The secondary objective was to evaluate other parameters of efficacy, such as DoR.

Table 15 : Summary of overall efficacy data (Induction Treatment Period) – Study CC-5013-NHL-008

	All subjects			**FL subjects**		
	Total N = 187[1]	Rituximab refractory: Yes N = 77	Rituximab refractory: No N = 110	Total N = 148	Rituximab refractory: Yes N = 60	Rituximab refractory: No N = 88
ORR, n (%) (CR+CRu+PR)	127 (67.9)	45 (58.4)	82 (75.2)	104 (70.3)	35 (58.3)	69 (79.3)
CRR, n (%) (CR+CRu)	79 (42.2)	27 (35.1)	52 (47.7)	62 (41.9)	20 (33.3)	42 (48.3)
Number of responders	**N = 127**	**N = 45**	**N = 82**	**N = 104**	**N = 35**	**N = 69**
% of subjects with DoR[2] ≥ 6 months (95% CI)[3]	**93.0 (85.1–96.8)**	**90.4 (73.0–96.8)**	**94.5 (83.9–98.2)**	**94.3 (85.5-97.9)**	**96.0 (74.8–99.4)**	**93.5 (81.0–97.9)**
% of subjects with DoR[2] ≥ 12 months (95% CI)[3]	**79.1 (67.4-87.0)**	**73.3 (51.2-86.6)**	**82.4 (67.5-90.9)**	**79.5 (65.5-88.3)**	**73.9 (43.0-89.8)**	**81.7 (64.8-91.0)**

CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; DoR = duration of response; FL = follicular lymphoma; ORR = overall response rate; PR= partial response.
[1] Primary analysis population for this study is induction efficacy evaluable (IEE) population.
[2] Duration of response is defined as the time (months) from the initial response (at least PR) to documented disease progression or death, whichever occurs first.

[3] Statistics obtained from Kaplan-Meier method. 95% CI is based on Greenwood formula.
Notes: The analysis is only performed for subjects who have achieved PR or better after the first dose date of induction therapy and prior to any maintenance period treatment and any subsequent anti-lymphoma therapy in induction period. Percentage is based on the total number of responders.

Paediatric population
The European Medicines Agency (EMA) has granted a product specific waiver for lenalidomide that applies to all subsets of the paediatric population for mature B-cell neoplasm conditions (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 (Cmax) 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 vs. time curve (AUC) and 50% decrease in Cmax in plasma. However, in the main multiple myeloma and MDS 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 multiple myeloma 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 5-25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers and ranges from 3 - 5 hours in patients with multiple myeloma, MDS or MCL

Elderly

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39-85 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 non-malignant conditions. In this study, 2 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 Cl_{Cr} > 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 × 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 (multiple myeloma, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

5.3 Preclinical safety data

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

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

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2,000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose
Cellulose, microcrystalline (E460 (i))
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigotine (E132)
Yellow iron oxide (E172)

Printing ink
Shellac (E904)
Propylene glycol (E1520)
Black iron oxide (E172)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

oPA/Al/PVC/Al blisters.
Boxes contain 7, 21 hard capsules.

Not all pack sizes may be marketed.

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.

Healthcare professional and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 4.4).

7 MARKETING AUTHORISATION HOLDER

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EC4A 1JP

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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