SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 2.5 mg, hard capsules
Revlimid 5 mg, hard capsules
Revlimid 7.5 mg, hard capsules
Revlimid 10 mg, hard capsules
Revlimid 15 mg, hard capsules
Revlimid 20 mg, hard capsules
Revlimid 25 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Revlimid 2.5 mg hard capsules
Each capsule contains 2.5 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 73.5 mg of lactose (as anhydrous lactose).

Revlimid 5 mg hard capsules
Each capsule contains 5 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 147 mg of lactose (as anhydrous lactose).

Revlimid 7.5 mg hard capsules
Each capsule contains 7.5 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 144.5 mg of lactose (as anhydrous lactose).

Revlimid 10 mg hard capsules
Each capsule contains 10 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 294 mg of lactose (as anhydrous lactose).

Revlimid 15 mg hard capsules
Each capsule contains 15 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 289 mg of lactose (as anhydrous lactose).

Revlimid 20 mg hard capsules
Each capsule contains 20 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 244.5 mg of lactose (as anhydrous lactose).

Revlimid 25 mg hard capsules
Each capsule contains 25 mg of lenalidomide.
Excipient(s) with known effect
Each capsule contains 200 mg of lactose (as anhydrous lactose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Revlimid 2.5 mg hard capsules
Blue-green/white capsules, size 4, 14.3 mm, marked “REV 2.5 mg”.

Revlimid 5 mg hard capsules
White capsules, size 2, 18.0 mm, marked “REV 5 mg”.

Revlimid 7.5 mg hard capsules
Pale yellow/white capsules, size 2, 18.0 mm, marked “REV 7.5 mg”.

Revlimid 10 mg hard capsules
Blue-green/pale yellow capsules, size 0, 21.7 mm, marked “REV 10 mg”.

Revlimid 15 mg hard capsules
Pale blue/white capsules, size 0, 21.7 mm, marked “REV 15 mg”.

Revlimid 20 mg hard capsules
Blue-green/pale blue capsules, size 0, 21.7 mm, marked “REV 20 mg”.

Revlimid 25 mg hard capsules
White capsules, size 0, 21.7 mm, marked “REV 25 mg”.

Because of the embryo-fetal risk, the marketing of Revlimid is subjected to a risk management plan (RMP), including the following:
• Prescribers guide. Prescribers must be certified with the REVLIMID RMP program by enrolling and complying with the RMP requirements.
• Patients brochure. Patient must sign a Patient-Physician agreement form and comply with the RMP requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception and males must comply with contraception requirements.
• Pharmacies must be certified within the REVLIMID RMP program. The medicine may only be dispensed to patients who are authorized to receive REVLIMID and comply with RMP requirements. Please ensure you are familiar with this important information and explain to the patient the need to review the brochures before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Multiple myeloma
Revlimid is indicated for the treatment of multiple myeloma.

Myelodysplastic syndromes
REVLIMID is indicated for patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Revlimid 7.5 mg is not indicated for treatment in MDS.

Mantle cell lymphoma
REVLIMID is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

Follicular lymphoma
Revlimid in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma.

4.2 Posology and method of administration

Revlimid 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 REVLIMID.
- 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)

- REVLIMID in combination with dexamethasone until disease progression in patients who are not eligible for transplant

REVLIMID treatment must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose
The recommended starting dose of REVLIMID is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1, 8, 15 and 22 of repeated 28-day cycles. Patients may continue REVLIMID and dexamethasone therapy until disease progression or intolerance.

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

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

[a] If Dose limiting toxicity (DLT) occurs on > day15 of a cycle, REVLIMID dosing will be interrupted for at least the remainder of the current 28-day cycle.

- *Absolute neutrophil count (ANC) - neutropenia*

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

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

For hematologic toxicity the dose of REVLIMID may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC ≥1,5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

- <u>REVLIMID in combination with bortezomib and dexamethasone followed by REVLIMID and dexamethasone until disease progression in patients who are not eligible for transplant</u>

Initial treatment: REVLIMID in combination with bortezomib and dexamethasone

REVLIMID in combination with bortezomib and dexamethasone must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

The recommended starting dose is REVLIMID 25 mg orally once daily days 1-14 of each 21-day cycle in combination with bortezomib and dexamethasone. Bortezomib should be administered via subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day.

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

Revlimid	**Bortezomib**	**Dexamethasone**
25 mg once daily on Days 1-14 of 21-day cycles	1.3 mg/m^2 on Days 1, 4, 8 and 11 of 21-day cycles	20 mg once daily orally on Days 1, 2, 4, 5, 8, 9, 11 and 12 of 21-day cycles

- <u>REVLIMID in combination with bortezomib and dexamethasone followed by REVLIMID and dexamethasone until disease progression in patients who are eligible for transplant</u>

Up to eight 21-day or six 28-day treatment cycles (24 weeks of initial treatment) are recommended.

Initial treatment: REVLIMID in combination with bortezomib and dexamethasone
REVLIMID in combination with bortezomib and dexamethasone must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Revlimid	**Bortezomib**	**Dexamethasone**
25 mg once daily on Days 1-14 of 21-day cycles	1.3 mg/m^2 on Days 1, 4, 8 and 11 of 21-day cycles	20 mg once daily on Days 1, 2, 4, 5, 8, 9, 11 and 12 of 21-day cycles
OR		
25 mg once daily on Days 1-21 of 28-day cycles	1.3 mg/m^2 on Days 1, 4, 8 and 11 of 28-day cycles	20 mg once daily on Days 1-4 and 9-12 of 28-day cycles

- *Continued treatment: Autologous stem cell transplant*

For patients who proceed to autologous stem cell transplant, hematopoietic stem cell mobilization should occur within 4 cycles of initial therapy.

Continued treatment: REVLIMID in combination with dexamethasone until progression
Continue REVLIMID 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*

	REVLIMID[a]
Starting dose	25 mg
Dose level -1	20 mg
Dose level -2	15 mg
Dose level -3	10 mg
Dose level- 4	5 mg
Dose level -5	5 mg every other day

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

When ANC	Recommended course[a]
First falls to < 0.5 x 10^9/L or febrile neutropenia [< 1.0 x 10^9/L associated with fever (temperature ≥ 38.5°C)]	Interrupt REVLIMID treatment
Returns to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume REVLIMID at starting dose once daily
Returns to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume REVLIMID at dose level -1 once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt REVLIMID treatment
Returns to ≥ 0.5 x 10^9/L	Resume REVLIMID at next lower dose level once daily.

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

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

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

Recommended dose

The recommended starting dose is REVLIMID 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1 to 4 of repeated 28-day cycles, prednisone 2 mg/kg orally on days 1 to 4 of repeated 28-day cycles. Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with REVLIMID monotherapy as follows: 10 mg orally once daily on days 1 to 21 of repeated 28-day cycles given until disease progression.

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

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

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

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

REVLIMID maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. REVLIMID must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

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

- *Dose reduction steps*

	Starting dose (10 mg)	If dose increased (15 mg)[a]
Dose level -1	5 mg	10 mg
Dose level -2	5 mg (days 1-21 every 28 days)	5 mg
Dose level -3	Not applicable	5 mg (days 1-21 every 28 days)
	Do not dose below 5 mg (days 1-21 every 28 days)	

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

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

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

Multiple myeloma with at least one prior therapy
REVLIMID treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

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

- *Dose reduction steps*

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

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

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

Myelodysplastic syndromes (MDS)

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

Recommended dose

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

- *Dose reduction steps*

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

When ANC	Recommended course
Falls to < 0.5 x 10^9/L Returns to ≥ 0.5 x 10^9/L	Interrupt REVLIMID treatment Resume REVLIMID at next lower dose level (dose level -1, -2 or -3)

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

Mantle cell lymphoma (MCL)
Recommended dose
The recommended starting dose of REVLIMID is 25 mg orally once daily on days 1 to 21 of repeated 28-day cycles.

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

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

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

Recommended dose
The recommended starting dose of REVLIMID is 20 mg, orally once daily on days 1 to 21 of repeated 28-day cycles for up to 12 cycles of treatment. The recommended starting dose of rituximab is 375 mg/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*

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

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

- *Thrombocytopenia*

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

- *Absolute neutrophil count (ANC) - neutropenia*

When ANC	Recommended course [a]
Falls < 1.0 x 10^9/L for at least 7 days or Falls to < 1.0 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Falls to < 0.5 x 10^9/L	Interrupt REVLIMID treatment and conduct CBC at least every 7 days
Returns to ≥ 1.0 x 10^9/L	Resume REVLIMID at next lower dose level (dose level -1)
For each subsequent drop below 1.0 x 10^9/L for at least 7 days or drop to < 1.0 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x 10^9/L	Interrupt REVLIMID treatment and conduct CBC at least every 7 days
Returns to ≥1.0 x 10^9/L	Resume REVLIMID at next lower dose level (dose level -2, -3). Do not dose below dose level-3

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

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

Tumour lysis syndrome (TLS)
All patients should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) and be well hydrated (orally) during the first week of the first cycle or for a longer period if clinically indicated. To monitor for TLS, patients should have a chemistry panel drawn weekly during the first cycle and as clinically indicated.
REVLIMID may be continued (maintain dose) in patients with laboratory TLS or Grade 1 clinical TLS, or at the physician's discretion, reduce dose by one level and continue REVLIMID. Vigorous intravenous 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 to 4 clinical TLS, interrupt REVLIMID and obtain a chemistry panel weekly or as clinically indicated. Vigorous intravenous 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 REVLIMID at next lower dose per physician's discretion (see section 4.4).

Tumour flare reaction
At the physician's discretion, REVLIMID may be continued in patients with Grade 1 or 2 tumour flare reaction (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 REVLIMID and initiate therapy with NSAIDs, corticosteroids and/or narcotic analgesics. When TFR resolves to ≤ Grade 1, restart REVLIMID 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 REVLIMID, 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.

REVLIMID interruption or discontinuation should be considered for Grade 2 or 3 skin rash. REVLIMID 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

Revlimid 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. REVLIMID has been used in clinical trials in multiple myeloma patients up to 91 years of age, in myelodysplastic syndromes patients up to 95 years of age and in mantle cell lymphoma patients up to 88 years of age (see section 5.1).

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it would be prudent to monitor renal function.

Newly diagnosed multiple myeloma: patients who are not eligible for transplant
Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

For patients older than 75 years of age treated with REVLIMID 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 REVLIMID in combination with melphalan and prednisone.

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

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

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

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

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

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

- Patients with renal impairment

REVLIMID is primarily excreted by the kidney; patients with greater degrees of renal impairment can have impaired treatment tolerance (see section 4.4). Care should be taken in dose selection and monitoring of renal function is advised.

No dose adjustments are required for patients with mild renal impairment and multiple myeloma, myelodysplastic syndromes, mantle cell lymphoma, or follicular lymphoma.
The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.
There are no phase 3 trial experiences with End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis).

Multiple myeloma

Renal function (CLcr)	**Dose adjustment**
Moderate renal impairment (30 ≤ CLcr < 50 mL/min)	10 mg once daily[1]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	7.5 mg once daily[2] 15 mg every other day

End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, the dose should be administered following dialysis.

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

Myelodysplastic syndromes

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

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

Mantle cell lymphoma

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

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

Follicular lymphoma

Renal function (CLcr)	**Dose adjustment** (days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30 ≤ CLcr < 60 mL/min)	10 mg once daily[1, 2]
Severe renal impairment (CLcr < 30 mL/min, not requiring dialysis)	No data available[3]
End Stage Renal Disease (ESRD) (CLcr < 30 mL/min, requiring dialysis)	No data available[3]

[1] The dose may be escalated to 15 mg once daily after 2 cycles if the patient has tolerated therapy.
[2] For patients on a starting dose of 10 mg, in case of dose reduction to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4. Toxicity judged to be related to REVLIMID do not dose below 5 mg every other day or 2.5 mg once daily.
[3] Patients with severe renal impairment or ESRD were excluded from study.

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

- Patients with hepatic impairment

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

Method of administration

Oral use.

Revlimid 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).

Females of childbearing potential may be treated with lenalidomide provided adequate precautions are taken to avoid pregnancy.

If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with REVLIMID must have pregnancy testing (sensitivity of at least 25 mIU/mL). The test should be performed prior to beginning therapy within 3 days prior to prescribing REVLIMID and then monthly thereafter (including dose interruptions). **Pregnancy testing should be performed also 4 weeks following discontinuation of REVLIMID therapy.**

Pregnancy testing and counseling must be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, REVLIMID must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

4.4 Special warnings and precautions for use

When REVLIMID is given in combination with other medicinal products, the corresponding Summary of Product Characteristics must be consulted prior to initiation of treatment.

Embryo-Fetal Toxicity
If REVLIMID is used during pregnancy, it may cause birth defects or death to a developing baby. Females of childbearing potential must be advised to avoid pregnancy while on REVLIMID. Two reliable forms of contraception should be used simultaneously during therapy, during dose interruptions and for at least 4 weeks following discontinuation of therapy.
There are no adequate and well-controlled studies in pregnant females.

REVLIMID can be prescribed only in agreement with RMP limitations.

Reproductive Risk and Special Prescribing Requirements (Revlimid RMP-PPP)
Revlimid can be prescribed and dispensed only if following the Revlimid Risk Management Program. All patients must follow the Revlimid Risk Minimization Program in order to receive Revlimid (refer to black box warning section)

Female Patients:
Two effective contraception methods must be used by female patients of childbearing potential for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for 4 weeks following discontinuation of REVLIMID therapy unless continuous abstinence from heterosexual sexual contact is the chosen method. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy, a bilateral oophorectomy, because the patient has been postmenopausal naturally for at least 24 consecutive months or in any other case indicated in Revlimid RMP. Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy, have not had a bilateral oophorectomy, who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) or in any other case indicated in the Revlimid RMP, are considered to be females of childbearing potential.

Cessation of menses due to anti-cancer therapy, do not exclude the potential to become pregnant.

Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method.
Females of childbearing potential must have a negative pregnancy test (sensitivity of at least 25 mIU/mL) before starting the therapy, and then monthly thereafter (including dose interruptions and including 4 weeks following discontinuation of REVLIMID therapy). The test should be performed within 3 days prior to prescribing REVLIMID. A prescription for REVLIMID for a female of childbearing potential must not be issued by the prescriber until a negative pregnancy test has been verified by the prescriber.
Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. REVLIMID therapy must be discontinued during this evaluation.
Pregnancy test results should be verified by the prescriber prior to dispensing **any** prescription.
If pregnancy does occur during treatment, REVLIMID must be discontinued immediately.
Any suspected fetal exposure to REVLIMID must be reported to the attending physician and Neopharm. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.
Do not breastfeed during therapy (including dose interruptions).

Patients should not donate blood while taking REVLIMID, during any breaks (discontinuations) in your therapy, and for 4 weeks following discontinuation of REVLIMID therapy.

Male Patients:
Clinical data has demonstrated the presence of REVLIMID in human semen. Therefore, males receiving REVLIMID must always use a latex/ polyurethane condom during any sexual contact with females of childbearing potential, even if they have undergone a successful vasectomy. In the case of a male patient with an allergy to latex or polyurethane, at least one highly effective form of contraception should be used by any female sexual partner. Contraception should be started in this partner at least 4 weeks prior to the start of a sexual relationship with the patient and continued throughout REVLIMID therapy including dose interruptions and for 4 weeks following discontinuation of therapy.
Patients should not donate blood and semen or sperm while taking REVLIMID, during any breaks (discontinuations) in your therapy, and for 4 weeks following discontinuation of REVLIMID therapy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should be performed every 4 weeks.

Pregnancy testing should be performed also 4 weeks following discontinuation of REVLIMID therapy.

Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks, and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks.

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.

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 health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day.

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

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of REVLIMID 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 REVLIMID in combination with melphalan and prednisone.

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with REVLIMID 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 REVLIMID in combination therapy (see sections 4.5 and 4.8).

In patients with multiple myeloma, the combination of REVLIMID 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 REVLIMID in combination with melphalan and prednisone. The risk of arterial thromboembolism is lower in patients with multiple myeloma treated with REVLIMID monotherapy than in patients with multiple myeloma treated with REVLIMID 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 REVLIMID 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 REVLIMID treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of REVLIMID treatment.

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

Neutropenia and thrombocytopenia
The major dose limiting toxicities of REVLIMID 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 REVLIMID treatment and monthly thereafter to monitor for cytopenias. In mantle cell lymphoma patients, the monitoring scheme should be every 2 weeks in cycles 3 and 4, and then at the start of each cycle. In follicular lymphoma, 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 REVLIMID with other myelosuppressive agents should be undertaken with caution.

- Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with REVLIMID 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 REVLIMID maintenance arms compared to the placebo maintenance arms in the 2 studies evaluating REVLIMID 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 REVLIMID 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 REVLIMID 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 REVLIMID maintenance arms compared to the placebo maintenance arms in studies evaluating REVLIMID maintenance in NDMM patients who have undergone ASCT (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively). Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).

- Newly diagnosed multiple myeloma: patients treated with REVLIMID in combination with bortezomib and dexamethasone

Grade 4 neutropenia was observed at a lower frequency in the REVLIMID 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%).

Increases in the incidence of Grade 3/ 4 adverse events in the RVd arm versus the Rd arm were most notable for peripheral sensory and motor neuropathy, thrombocytopenia, hypotension, diarrhoea, syncope, hypokalaemia and dehydration.

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

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

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

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

The combination of REVLIMID with melphalan and prednisone in clinical trials of newly diagnosed multiple myeloma patients is associated with a higher incidence of Grade 4 neutropenia (34.1% in melphalan, prednisone and REVLIMID arm followed by REVLIMID [MPR+R] and melphalan, prednisone and REVLIMID 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 REVLIMID with melphalan and prednisone in multiple myeloma patients is associated with a higher incidence of Grade 3 and Grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p treated patients, compared with 13.7% in MPp+p-treated patients; see section 4.8).

- Multiple myeloma: patients with at least one prior therapy

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

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

- Myelodysplastic syndromes

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

- Mantle cell lymphoma

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

- Follicular lymphoma

The combination of REVLIMID with rituximab in follicular lymphoma 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 REVLIMID/ 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
REVLIMID is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with REVLIMID in combination with dexamethasone or melphalan and prednisone or REVLIMID monotherapy or with long term use of REVLIMID for the treatment of newly diagnosed multiple myeloma.

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

Tumour flare reaction and tumour lysis syndrome
Because REVLIMID 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 REVLIMID. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken.

- Mantle cell lymphoma

Careful monitoring and evaluation for TFR is recommended. Patients with high mantle cell lymphoma International Prognostic Index (MIPI) at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. Tumour flare reaction may mimic progression of disease (PD). Patients in studies MCL-002 and MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, NSAIDs and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient (see sections 4.2 and 4.8).

- Follicular lymphoma

Careful monitoring and evaluation for TFR is recommended. Tumour flare may mimic PD. Patients who experienced Grade 1 and 2 TFR were treated with corticosteroids, NSAIDs and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of 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
- Mantle cell lymphoma

REVLIMID 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 REVLIMID 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 REVLIMID 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 REVLIMID arm was adverse events, 7/11 (64%).
Patients with high tumour burden should therefore be closely monitored for adverse reactions (see Section 4.8) including signs of tumour flare reaction (TFR). Please refer to section 4.2 for dose adjustments for TFR.
High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

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 REVLIMID (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. REVLIMID 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 REVLIMID 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 REVLIMID and thalidomide has been reported in the literature. Patients with a history of severe rash associated with thalidomide treatment should not receive REVLIMID.

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

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

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving REVLIMID 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 REVLIMID (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 REVLIMID in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

A 1.3-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving REVLIMID in combination with dexamethasone until progression or for 18 months (1.58 per 100 person-years) compared to thalidomide in combination with melphalan and prednisone (1.19 per 100 person-years).

In newly diagnosed multiple myeloma patients receiving REVLIMID in combination with bortezomib and dexamethasone, the hematologic SPM incidence rate was 0.00 – 0.16 per 100 person-years and the incidence rate of solid tumour SPM was 0.21 – 1.04 per 100 person-years.

The increased risk of secondary primary malignancies associated with REVLIMID is relevant also in the context of NDMM after stem cell transplantation. Though this risk is not yet fully characterized, it should be kept in mind when considering and using Revlimid in this setting.

The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma), was 1.31 per 100 person-years for the REVLIMID arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to REVLIMID after ASCT and 0.60 per 100 person-years for patients not-exposed to REVLIMID after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the REVLIMID arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to REVLIMID after ASCT and 0.60 per 100 person-years for patients not-exposed to REVLIMID after ASCT).

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

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

- Karyotype

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

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

- TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of REVLIMID in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27.5 % in patients with IHC-p53 positivity (1% cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3.6% in patients with IHC-p53 negativity (p=0.0038) (see section 4.8)

Progression to other malignancies in mantle cell lymphoma

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

Second primary malignancies in follicular lymphoma

In a relapsed/refractory iNHL study which included follicular lymphoma patients, no increased risk of SPMs in the REVLIMID/rituximab arm, compared to the placebo/rituximab arm, was observed. Hematologic SPM of AML occurred in 0.29 per 100 person-years in the REVLIMID/rituximab arm compared with 0.29 per 100 person-years in patients receiving placebo/rituximab. The incidence rate of hematologic plus solid tumour SPMs (excluding non-melanoma skin cancers) was 0.87 per 100 person-years in the REVLIMID/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 to 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 REVLIMID and the risk of SPMs should be considered when considering treatment with REVLIMID.

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with REVLIMID 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.

REVLIMID 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 REVLIMID 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 REVLIMID in combination with dexamethasone than with MPT in patients with NDMM who are not eligible for transplant, and with REVLIMID 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 REVLIMID, 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 REVLIMID and adequate antiviral treatment.

Reactivation of hepatitis B has been reported rarely in patients receiving REVLIMID who have previously been infected with the hepatitis B virus. Some of these cases have progressed to acute hepatic failure resulting in discontinuation of REVLIMID and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with REVLIMID. 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 REVLIMID 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 REVLIMID. PML was reported several months to several years after starting the treatment with REVLIMID. 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, REVLIMID must be permanently discontinued.

Newly diagnosed multiple myeloma patients
There was a higher rate of intolerance (Grade 3 or 4 adverse events, serious adverse events, discontinuation) in patients with age > 75 years, ISS stage III, ECOG PS≥2 or CLcr<60 mL/min when REVLIMID is given in combination. Patients should be carefully assessed for their ability to tolerate REVLIMID in combination, with consideration to age, ISS stage III, ECOG PS≥2 or CLcr<60 mL/min (see sections 4.2 and 4.8).

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

4.5 Interaction with other medicinal products and other forms of interaction

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving REVLIMID with dexamethasone (see sections 4.4 and 4.8).

Oral contraceptives
No interaction study has been performed with oral contraceptives. REVLIMID is not an enzyme inducer. In an *in vitro* study with human hepatocytes, REVLIMID, 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 REVLIMID 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 REVLIMID 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 REVLIMID. 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 REVLIMID 10 mg once daily increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the clinical use (higher REVLIMID doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during REVLIMID treatment.

Statins
There is an increased risk of rhabdomyolysis when statins are administered with REVLIMID, 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 REVLIMID (25 mg once daily).
Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, REVLIMID 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 REVLIMID (25 mg). Co-administration of REVLIMID does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

Due to the teratogenic potential, REVLIMID 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 REVLIMID, 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 REVLIMID, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

REVLIMID 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 REVLIMID should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy
REVLIMID is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

REVLIMID induced malformation in monkeys similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of REVLIMID is expected and REVLIMID is contraindicated during pregnancy (see section 4.3).

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

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

and no parental toxicity.

4.7 Effects on ability to drive and use machines

REVLIMID 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 REVLIMID. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with REVLIMID 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 REVLIMID 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 REVLIMID 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 REVLIMID 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%]).

Newly diagnosed multiple myeloma patients receiving REVLIMID in combination with bortezomib and dexamethasone

In the SWOG S0777 study, the serious adverse reactions observed more frequently (≥ 5%) with REVLIMID in combination with intravenous bortezomib and dexamethasone than with REVLIMID in combination with dexamethasone were:

- Hypotension (6.5%), lung infection (5.7%), dehydration (5.0%)

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

The most frequent adverse events with the Revlimid, bortezomib and dexamethasone combination across the 3 studies were in the System Organ Classes of Nervous System Disorders, Blood and Lymphatic System Disorders and Gastrointestinal Disorders. Compared with Revlimid and dexamethasone, the combination of Revlimid, bortezomib and dexamethasone was associated with increased incidences of treatment-emergent serious adverse events (40.1% RVd vs. 28.5% Rd) and discontinuations due to treatment emergent AEs (22.9% RVd vs. 9.4% Rd). Increases in the incidence of

Grade 3/ 4 adverse events in the RVd arm versus the Rd arm were most notable for peripheral sensory and motor neuropathy, thrombocytopenia, hypotension, diarrhoea, syncope, hypokalaemia and dehydration.

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

The serious adverse reactions observed more frequently (≥5%) with REVLIMID in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were:

- Pneumonia (9.8%)
- Renal failure (including acute) (6.3%)

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

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

The serious adverse reactions observed more frequently (≥5%) with melphalan, prednisone and REVLIMID followed by REVLIMID maintenance (MPR+R) or melphalan, prednisone and REVLIMID 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 one prior therapy

In two phase 3 placebo-controlled studies, 353 patients with multiple myeloma were exposed to the REVLIMID/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in REVLIMID/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 REVLIMID 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%).

Myelodysplastic syndromes

The overall safety profile of REVLIMID in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one phase 2 study and one phase 3 study (see section 5.1). In the phase 2, all 148 patients were on REVLIMID treatment. In the phase 3 study, 69 patients were on REVLIMID 5 mg, 69 patients on REVLIMID 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 REVLIMID.

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 REVLIMID groups compared to the control arm in the phase 3 study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhoea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).

Mantle cell lymphoma
The overall safety profile of Revlimid in patients with mantle cell lymphoma is based on data from 254 patients from a phase 2 randomised, controlled study MCL-002 (see section 5.1).
Additionally, adverse drug reactions from supportive study MCL-001 have been included in table 3.

The serious adverse reactions observed more frequently in study MCL-002 (with a difference of at least 2 percentage points) in the REVLIMID 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 REVLIMID 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 REVLIMID 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 REVLIMID 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 REVLIMID arm was adverse events, 7/11 (64%). High tumour burden was defined as at least one lesion ≥5 cm in diameter or 3 lesions ≥3 cm.

Follicular lymphoma
The overall safety profile of REVLIMID in combination with rituximab in patients with previously treated follicular lymphoma is based on data from 294 patients from a Phase 3 randomised, controlled study NHL-007.
Additionally, adverse drug reactions from supportive study NHL-008 have been included 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 REVLIMID/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 REVLIMID/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 Revlimid are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

Tabulated summary for monotherapy in MM

The following table is derived from data gathered during NDMM studies in patients who have undergone ASCT treated with REVLIMID maintenance. The data were not adjusted according to the longer duration of treatment in the REVLIMID-containing arms continued until disease progression versus the placebo arms in the pivotal multiple myeloma studies (see section 5.1).

Table 1. ADRs reported in clinical trials in patients with multiple myeloma treated with REVLIMID maintenance therapy

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia[◊,a], Upper respiratory tract infection, Neutropenic infection, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Sinusitis, Nasopharyngitis, Rhinitis Common Infection[◊], Urinary tract infection[◊,*], Lower respiratory tract infection, Lung infection[◊]	Very Common Pneumonia[◊,a], Neutropenic infection Common Sepsis[◊,b], Bacteraemia, Lung infection[◊], Lower respiratory tract infection bacterial, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Herpes zoster[◊], Infection[◊]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome[◊,*]	
Blood and Lymphatic System Disorders	Very Common Neutropenia[^,◊], Febrile neutropenia[^,◊], Thrombocytopenia[^,◊], Anaemia, Leucopenia[◊], Lymphopenia	Very Common Neutropenia[^,◊], Febrile neutropenia[^,◊], Thrombocytopenia[^,◊], Anaemia, Leucopenia[◊], Lymphopenia Common Pancytopenia[◊]
Metabolism and Nutrition Disorders	Very Common Hypokalaemia	Common Hypokalaemia, Dehydration
Nervous System Disorders	Very Common Paraesthesia Common Peripheral neuropathy[c]	Common Headache
Vascular Disorders	Common	Common

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
	Pulmonary embolism[◊,*]	Deep vein thrombosis[^,◊,d]
Respiratory, Thoracic and Mediastinal Disorders	Very Common Cough Common Dyspnoea[◊], Rhinorrhoea	Common Dyspnoea[◊]
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash, Dry skin	Common Rash, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms Common Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue, Asthenia

[◊] Adverse reactions reported as serious in clinical trials in patients with NDMM who had undergone ASCT
[*] Applies to serious adverse drug reactions only
[^] See section 4.8 description of selected adverse reactions
[a] "Pneumonia" combined AE term includes the following PTs: Bronchopneumonia, Lobar pneumonia, Pneumocystis jiroveci pneumonia, Pneumonia, Pneumonia klebsiella, Pneumonia legionella, Pneumonia mycoplasmal, Pneumonia pneumococcal, Pneumonia streptococcal, Pneumonia viral, Lung disorder, Pneumonitis
[b] "Sepsis" combined AE term includes the following PTs: Bacterial sepsis, Pneumococcal sepsis, Septic shock, Staphylococcal sepsis
[c] "Peripheral neuropathy" combined AE term includes the following preferred terms (PTs): Neuropathy peripheral, Peripheral sensory neuropathy, Polyneuropathy
[d] "Deep vein thrombosis" combined AE term includes the following PTs: Deep vein thrombosis, Thrombosis, Venous thrombosis

Tabulated summary for combination therapy in MM

The following table is derived from data gathered during the multiple myeloma studies with combination therapy. The data were not adjusted according to the longer duration of treatment in the REVLIMID-containing arms continued until disease progression versus the comparator arms in the pivotal multiple myeloma studies (see section 5.1).

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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia[◊,◊◊], Upper respiratory tract infection[◊], Bacterial, viral and fungal infections (including opportunistic infections)[◊], Nasopharyngitis, Pharyngitis, Bronchitis[◊], Rhinitis Common Sepsis[◊,◊◊], Lung infection[◊◊], Urinary tract infection[◊◊], Sinusitis[◊]	Common Pneumonia[◊,◊◊], Bacterial, viral and fungal infections (including opportunistic infections)[◊], Cellulitis[◊], Sepsis[◊,◊◊], Lung infection[◊◊], Bronchitis[◊], Respiratory tract infection[◊◊], Urinary tract infection[◊◊], Enterocolitis infectious
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma[^,◊], Squamous skin cancer[^,◊,*]	Common Acute myeloid leukaemia[◊], Myelodysplastic syndrome[◊], Squamous cell carcinoma of skin[^,◊,**] Uncommon T-cell type acute leukaemia[◊], Basal cell carcinoma[^,◊], Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia[^,◊,◊◊], Thrombocytopenia[^,◊,◊◊], Anaemia[◊], Haemorrhagic disorder[^], Leucopenia, Lymphopenia Common Febrile neutropenia[^,◊], Pancytopenia[◊] Uncommon Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	Very Common Neutropenia[^,◊,◊◊], Thrombocytopenia[^,◊,◊◊], Anaemia[◊], Leucopenia, Lymphopenia Common Febrile neutropenia[^,◊], Pancytopenia[◊], Haemolytic anaemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity[^]	
Endocrine Disorders	Common Hypothyroidism	

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Metabolism and Nutrition Disorders	Very Common Hypokalaemia[◊,◊◊], Hyperglycaemia, Hypoglycaemia, Hypocalcaemia[◊], Hyponatraemia[◊], Dehydration[◊◊], Decreased appetite[◊◊], Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Hypercalcaemia[+]	Common Hypokalaemia[◊,◊◊], Hyperglycaemia, Hypocalcaemia[◊], Diabetes mellitus[◊], Hypophosphataemia, Hyponatraemia[◊], Hyperuricaemia, Gout, Dehydration[◊◊], Decreased appetite[◊◊], Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
Nervous System Disorders	Very Common Peripheral neuropathies[◊◊], Paraesthesia, Dizziness[◊◊], Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired, Syncope[◊◊], Neuralgia, Dysaesthesia	Very Common Peripheral neuropathies[◊◊] Common Cerebrovascular accident[◊], Dizziness[◊◊], Syncope[◊◊], Neuralgia Uncommon Intracranial haemorrhage[^,], Transient ischaemic attack, Cerebral ischemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation[◊,◊◊], Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute)[^,◊], Atrial fibrillation[◊,◊◊], Congestive cardiac failure[◊], Tachycardia, Cardiac failure[◊,◊◊], Myocardial ischemia[◊]

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Vascular Disorders	Very Common Venous thromboembolic events[^], predominantly deep vein thrombosis and pulmonary embolism[^,◊,◊◊], Hypotension[◊◊] Common Hypertension, Ecchymosis[^]	Very Common Venous thromboembolic events[^], predominantly deep vein thrombosis and pulmonary embolism[^,◊,◊◊] Common Vasculitis, Hypotension[◊◊], Hypertension Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea[◊,◊◊], Epistaxis^, Cough Common Dysphonia	Common Respiratory distress[◊], Dyspnoea[◊,◊◊], Pleuritic pain[◊◊], Hypoxia[◊◊]
Gastrointestinal Disorders	Very Common Diarrhoea[◊,◊◊], Constipation[◊], Abdominal pain[◊◊], Nausea, Vomiting[◊◊], Dyspepsia, Dry mouth, Stomatitis Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)[^,◊◊], Dysphagia Uncommon Colitis, Caecitis	Common Gastrointestinal haemorrhage[^,◊,◊◊], Small intestinal obstruction[◊◊], Diarrhoea[◊◊], Constipation[◊], Abdominal pain[◊◊], Nausea, Vomiting[◊◊]
Hepatobiliary Disorders	Very Common Alanine aminotransferase increased, Aspartate aminotransferase increased Common Hepatocellular injury[◊◊], Abnormal liver function tests[◊], Hyperbilirubinaemia Uncommon Hepatic failure[^]	Common Cholestasis[◊], Hepatotoxicity, Hepatocellular injury[◊◊], Alanine aminotransferase increased, Abnormal liver function tests[◊] Uncommon Hepatic failure[^]

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Skin and Subcutaneous Tissue Disorders	Very Common Rashes[◊◊], Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Drug rash with eosinophilia and systemic symptoms[◊◊], Skin discolouration, Photosensitivity reaction	Common Rashes[◊◊] Uncommon Drug rash with eosinophilia and systemic symptoms[◊◊]
Musculoskeletal and Connective Tissue Disorders	Very Common Muscular weakness[◊◊], Muscle spasms, Bone pain[◊], Musculoskeletal and connective tissue pain and discomfort (including back pain[◊,◊◊]), Pain in extremity, Myalgia, Arthralgia[◊] Common Joint swelling	Common Muscular weakness[◊◊], Bone pain[◊], Musculoskeletal and connective tissue pain and discomfort (including back pain[◊,◊◊]) Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute)[◊,◊◊] Common Haematuria[^], Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue[◊,◊◊], Oedema (including peripheral oedema), Pyrexia[◊,◊◊], Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain[◊,◊◊], Lethargy	Very Common Fatigue[◊,◊◊] Common Oedema peripheral, Pyrexia[◊,◊◊], Asthenia
Investigations	Very Common Blood alkaline phosphatase increased Common C-reactive protein increased	

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Injury, Poisoning and Procedural Complications	Common Fall, Contusion^	

◊◊Adverse reactions reported as serious in clinical trials in patients with NDMM who had received REVLIMID in combination with bortezomib and dexamethasone
^See section 4.8 description of selected adverse reactions
◊ Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with REVLIMID in combination with dexamethasone, or with melphalan and prednisone
+ Applies to serious adverse drug reactions only
* Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with REVLIMID/dexamethasone compared to controls
** Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with REVLIMID/dexamethasone compared to controls

Tabulated summary from monotherapy

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

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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)◊	Very Common Pneumonia◊ Common Bacterial, viral and fungal infections (including opportunistic infections)◊, Bronchitis
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Leucopenia	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Leucopenia Common Febrile neutropenia^,◊
Endocrine Disorders	Very Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Decreased appetite Common Iron overload, Weight decreased	Common Hyperglycaemia◊, Decreased appetite
Psychiatric Disorders		Common Altered mood◊,~
Nervous System Disorders	Very Common Dizziness, Headache Common Paraesthesia	

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Cardiac Disorders		Common Acute myocardial infarction^,◊, Atrial fibrillation◊, Cardiac failure◊
Vascular Disorders	Common Hypertension, Haematoma	Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊
Respiratory, Thoracic and Mediastinal Disorders	Very Common Epistaxis^	
Gastrointestinal Disorders	Very Common Diarrhoea◊, Abdominal pain (including upper), Nausea, Vomiting, Constipation Common Dry mouth, Dyspepsia	Common Diarrhoea◊, Nausea, Toothache
Hepatobiliary Disorders	Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Dry Skin, Pruritus	Common Rashes, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Musculoskeletal pain (including back pain◊ and pain in extremity), Arthralgia, Myalgia	Common Back pain◊
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)	Common Pyrexia
Injury, Poisoning and Procedural Complications		Common Fall

^see section 4.8 description of selected adverse reactions

◊Adverse events reported as serious in myelodysplastic syndromes clinical trials

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

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

Algorithm applied for myelodysplastic syndromes:

- Myelodysplastic syndromes phase 3 study (double-blind safety population, difference between REVLIMID 5/10mg and placebo by initial dosing regimen occurring in at least 2 subjects)
    - All treatment-emergent adverse events with ≥ 5% of subjects in REVLIMID and at least 2% difference in proportion between REVLIMID and placebo
    - All treatment-emergent Grade 3 or 4 adverse events in 1% of subjects in REVLIMID and at least 1% difference in proportion between REVLIMID and placebo
    - All treatment-emergent serious adverse events in 1% of subjects in REVLIMID and at least 1% difference in proportion between REVLIMID and placebo
- Myelodysplastic syndromes phase 2 study
    - All treatment-emergent adverse events with ≥ 5% of REVLIMID treated subjects
    - All treatment-emergent Grade 3 or 4 adverse\events in 1% of REVLIMID treated subjects
    - All treatment-emergent serious adverse events in 1% of REVLIMID treated subjects

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

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Very Common Bacterial, viral and fungal infections (including opportunistic infections)[◊], Nasopharyngitis, Pneumonia[◊] Common Sinusitis	Common Bacterial, viral and fungal infections (including opportunistic infections)[◊], Pneumonia[◊]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Tumour flare reaction	Common Tumour flare reaction, Squamous skin cancer[^,◊], Basal cell carcinoma[^,◊]
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia[^], Neutropenia[^,◊], Leucopenia[◊], Anaemia[◊] Common Febrile neutropenia[^,◊]	Very Common Thrombocytopenia[^], Neutropenia[^,◊], Anaemia[◊] Common Febrile neutropenia[^,◊], Leucopenia[◊]
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Weight decreased, Hypokalaemia Common Dehydration[◊]	Common Dehydration[◊], Hyponatraemia, Hypocalcaemia
Psychiatric Disorders	Common Insomnia	
Nervous System Disorders	Common Dysgeuesia, Headache, neuropathy peripheral	Common Peripheral sensory neuropathy, Lethargy
Ear and Labyrinth Disorders	Common Vertigo	
Cardiac Disorders		Common Myocardial infarction (including acute)[^,◊], Cardiac failure
Vascular Disorders	Common Hypotension[◊]	Common Deep vein thrombosis[◊], pulmonary embolism[^,◊], Hypotension[◊]
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea[◊]	Common Dyspnoea[◊]

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Gastrointestinal Disorders	Very Common Diarrhoea◊, Nausea◊, Vomiting◊, Constipation Common Abdominal pain◊	Common Diarrhoea◊, Abdominal pain◊, Constipation
Skin and Subcutaneous Tissue Disorders	Very Common Rashes (including dermatitis allergic), Pruritus Common Night sweats, Dry skin	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain Common Arthralgia, Pain in extremity, Muscular weakness◊	Common Back pain, Muscular weakness◊, Arthralgia, Pain in extremity
Renal and Urinary Disorders		Common Renal failure◊
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia◊, Peripheral oedema, Influenza like illness syndrome (including pyrexia◊, cough) Common Chills	Common Pyrexia◊, Asthenia◊, Fatigue

^see section 4.8 description of selected adverse reactions

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

- Mantle cell lymphoma controlled phase 2 study
  - All treatment-emergent adverse events with ≥ 5% of subjects in REVLIMID arm and at least 2% difference in proportion between REVLIMID and control arm
  - All treatment-emergent Grade 3 or 4 adverse events in ≥1% of subjects in REVLIMID arm and at least 1.0% difference in proportion between REVLIMID and control arm
  - All Serious treatment-emergent adverse events in ≥1% of subjects in REVLIMID arm and at least 1.0% difference in proportion between REVLIMID and control arm
- Mantle cell lymphoma single arm phase 2 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

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 REVLIMID in combination with rituximab for patients with follicular lymphoma.

Table 5. ADRs reported in clinical trials in patients with follicular lymphoma treated with REVLIMID 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[◊], Influenza, Bronchitis, Sinusitis, Urinary tract infection	Common Pneumonia[◊], Sepsis[◊], Lung infection, Bronchitis, Gastroenteritis, Sinusitis, Urinary tract infection, Cellulitis[◊]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Very Common Tumour flare[^] Common Squamous Cell Carcinoma of Skin[◊,^,+]	Common Basal cell carcinoma[^,◊]
Blood and Lymphatic System Disorders	Very Common Neutropenia[^,◊], Anaemia[◊], Thrombocytopenia[^], Leucopenia[**] Lymphopenia[***]	Very Common Neutropenia[^,◊] Common Anaemia[◊], Thrombocytopenia[^], Febrile neutropenia[◊], Pancytopenia, Leucopenia[**], Lymphopenia[***]
Metabolism and Nutrition Disorders	Very Common Decreased appetite, Hypokalaemia Common Hypophosphataemia, Dehydration	Common Dehydration, Hypercalcaemia[◊], Hypokalaemia, Hypophosphataemia, Hyperuricaemia
Psychiatric Disorders	Common Depression, Insomnia	
Nervous System Disorders	Very Common Headache, Dizziness Common Peripheral sensory neuropathy, Dysgeusia	Common Syncope
Cardiac Disorders	Uncommon Arrhythmia[◊]	
Vascular Disorders	Common Hypotension	Common Pulmonary embolism[^,◊], Hypotension
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea[◊], Cough, Common Oropharyngeal pain, Dysphonia	Common Dyspnoea[◊]
Gastrointestinal Disorders	Very Common Abdominal pain[◊], Diarrhoea, Constipation, Nausea, Vomiting, Dyspepsia Common Upper abdominal pain, Stomatitis, Dry mouth	Common Abdominal pain[◊], Diarrhoea, Constipation, Stomatitis
Skin and Subcutaneous Tissue Disorders	Very Common Rash[*], Pruritus Common Dry skin, Night sweats, Erythema	Common Rash[*], Pruritus

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Back pain, Arthralgia Common Pain in extremity, Muscular weakness, Musculoskeletal pain, Myalgia, Neck pain	Common Muscular weakness, Neck pain
Renal and Urinary Disorders		Common Acute kidney injury◊
General Disorders and Administration Site Conditions	Very Common Pyrexia, Fatigue, Asthenia, Peripheral oedema Common Malaise, Chills	Common Fatigue, Asthenia
Investigations	Very Common Alanine aminotransferase increased Common Weight decreased, Blood Bilirubin increased	

^see section 4.8 description of selected adverse reactions
Algorithm applied for follicular lymphoma:
Controlled– Phase 3 trial:

- NHL-007 ADRs- All treatment-emergent AEs with ≥ 5.0% of subjects in REVLIMID/rituximab arm and at least 2.0% higher frequency (%) in Len arm compared to control arm - (Safety population)
- NHL-007 Gr 3/4 ADRs- All Grades 3 or Grade 4 treatment-emergent AEs with at least 1.0% subjects in REVLIMID/rituximab arm and at least 1.0% higher frequency in REVLIMID arm compared to control arm - (safety population)
- NHL-007 Serious ADRs- All serious treatment-emergent AEs with at least 1.0% subjects in REVLIMID/rituximab arm and at least 1.0% higher frequency in REVLIMID/rituximab arm compared to control arm - (safety population)

FL single arm - phase 3 trial:

- NHL-008 ADRs- All treatment-emergent adverse events with ≥ 5.0% of subjects
- NHL-008 Gr 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

◊Adverse events reported as serious in follicular lymphoma clinical trials
+ Applies to serious adverse drug reactions only
* Rash includes PT of rash and rash maculo-papular
**Leucopenia includes PT leucopenia and white blood cell count decreased
***Lymphopenia includes PT lymphopenia and lymphocyte count decreased

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 REVLIMID

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	Not Known Viral infections, including herpes zoster and hepatitis B virus reactivation	Not Known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Rare Tumour lysis syndrome

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Blood and Lymphatic System Disorders	Not Known Acquired haemophilia	
Immune System Disorders	Rare Anaphylactic reaction^ Not Known Solid organ transplant rejection	Rare Anaphylactic reaction^
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)^
Hepatobiliary Disorders	Not Known Acute hepatic failure^, Hepatitis toxic^, Cytolytic hepatitis^, Cholestatic hepatitis^, Mixed cytolytic/cholestatic hepatitis^	Not Known Acute hepatic failure^, Hepatitis toxic^
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome^, Toxic epidermal necrolysis^ Not Known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms^

^see section 4.8 description of selected adverse reactions

Description of selected adverse reactions

Teratogenicity

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

Neutropenia and thrombocytopenia

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

REVLIMID 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 REVLIMID 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 REVLIMID 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).

REVLIMID maintenance after ASCT is associated with a higher frequency of Grade 3 or 4 thrombocytopenia compared to placebo maintenance (37.5% vs 30.3% [17.9% vs 4.1% after the start of maintenance treatment] in CALGB 100104 and 13.0% vs 2.9% in IFM 2005-02, respectively).

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

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

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

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

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

The combination of REVLIMID with dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of Grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18) compared with MPT (11.1%).

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

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

The combination of REVLIMID with melphalan and prednisone in newly diagnosed multiple myeloma patients is associated with a higher frequency of Grade 3 and Grade 4 thrombocytopenia (40.4% in MPR+R/MPR+p) compared with MPp+p (13.7%).

- Multiple myeloma: patients with at least one prior therapy

The combination of REVLIMID with dexamethasone in multiple myeloma patients is associated with a higher incidence of Grade 4 neutropenia (5.1% in REVLIMID/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in REVLIMID/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

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

- Myelodysplastic syndromes patients

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

- Mantle cell lymphoma patients

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

- Follicular lymphoma patients

The combination of REVLIMID with rituximab in follicular lymphoma is associated with a higher rate of grade 3 or grade 4 neutropenia (50.7% in REVLIMID/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 REVLIMID/rituximab treated patients compared with 0.7% in placebo/rituximab treated patients).

REVLIMID in combination with rituximab is also associated with a higher incidence of grade 3 or 4 thrombocytopenia (1.4% in REVLIMID/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 REVLIMID with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with REVLIMID in combination with melphalan and prednisone or in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma treated with REVLIMID 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 REVLIMID, 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 aller*gic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of REVLIMID. A possible cross-reaction

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

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

Acute myeloid leukaemia
- Multiple myeloma

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

- Myelodysplastic syndromes

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

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

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

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

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

In study NHL-007, TFR was reported in 19/146 (13.0%) of patients in the REVLIMID/rituximab arm versus 1/148 (0.7%) patients in the placebo/rituximab arm. Most TFRs (18 out of 19) reported in the REVLIMID/rituximab arm occurred during first two cycles of treatment. One FL patient in the REVLIMID/rituximab arm experienced a Grade 3 TFR event versus 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 REVLIMID/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 REVLIMID/rituximab therapy due to TFR or TLS.

Gastrointestinal disorders
Gastrointestinal perforations have been reported during treatment with REVLIMID. 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

There is no specific experience in the management of REVLIMID 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
REVLIMID 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, REVLIMID 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, REVLIMID inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), REVLIMID selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.
The combination of REVLIMID and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells.
The REVLIMID mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. REVLIMID 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

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

Newly diagnosed multiple myeloma

- *REVLIMID maintenance in patients who have undergone ASCT*

The efficacy and safety of REVLIMID maintenance was assessed in two phase 3 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 MM requiring treatment and without prior progression after initial treatment were eligible.

Patients were randomised 1:1 within 90-100 days after ASCT to receive either REVLIMID 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 REVLIMID and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

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

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 17 December 2009 (15.5 months follow up) showed a 62% reduction in risk of disease progression or death favouring REVLIMID (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 REVLIMID arm versus 19.0 months (95% CI 16.2, 25.6) in the placebo arm.

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

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

Table 7. Summary of overall efficacy data

	REVLIMID (N = 231)	Placebo (N = 229)
Investigator-assessed PFS		
Median[a] PFS time, months (95% CI)[b]	**56.9** (41.9, 71.7)	**29,4** (20.7, 35.5)
HR [95% CI][c]; p-valued	**0.61** (0.48, 0.76); <0.001	
PFS2[e]		
Median[a] PFS2 time, months (95% CI)[b]	**80.2** (63.3, 101.8)	**52.8** (41.3, 64.0)
HR [95% CI]c ; p-valued	**0.61** (0.48, 0.78); <0.001	
Overall survival		
Median[a] OS time, months (95% CI)[b]	**111.0** (101.8, NE)	**84.2** (71.0, 102.7)
8-year survival rate, % (SE)	60.9 (3.78)	44.6 (3.98)

	REVLIMID (N = 231)	Placebo (N = 229)
HR [95% CI][c] ; p-value[d]	**0.61** (0.46, 0.81); <0.001	
Follow-up		
Median[f] (min, max), months: all surviving patients	**81.9** (0.0, 119.8)	**81.0** (4.1, 119.5)

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

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

[b] The 95% CI about the median.

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

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

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

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

Data cuts: 17 Dec 2009 and 01 Feb 2016

IFM 2005-02

Patients aged < 65 years at diagnosis who had undergone ASCT and had achieved at least a stable disease response at the time of hematologic recovery were eligible. Patients were randomised 1:1 to receive either REVLIMID 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 REVLIMID 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 REVLIMID and 307 patients to placebo.

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

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 7 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favouring REVLIMID (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 REVLIMID arm versus 22.8 months (95% CI 20.7, 27.4) in the placebo arm.

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

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

- <u>REVLIMID in combination with bortezomib and dexamethasone in patients who are not eligible for stem cell transplantation</u>

The SWOG S0777 study evaluated the addition of bortezomib to a foundation of REVLIMID 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 REVLIMID, bortezomib and dexamethasone (RVd) arm received REVLIMID 25 mg/day orally on days 1-14, intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of repeated 21-day cycles for up to eight 21-day cycles (24 weeks). Patients in the REVLIMID and dexamethasone (Rd) arm received REVLIMID 25 mg/day orally on days 1-21, and dexamethasone 40 mg/day orally on days 1, 8, 15, and 22 of repeated 28-day cycles for up to six 28-day cycles (24 weeks). Patients in both arms took continued Rd: REVLIMID 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 versus 29.9 months (95% CI 25.6, 38.2) in the Rd arm. The benefit was observed regardless of eligibility for stem cell transplant.

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

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[a] PFS time, months (95% CI)[b]	**41.7** (33.1, 51.5)	**29.7** (24.2, 37.8)
HR [95% CI][c]; p-value[d]	**0.76** (0.62, 0.94); 0.010	
Overall survival (months)		
Median[a] OS time, months (95% CI)[b]	**89.**1 (76.1, NE)	**67.2** (58.4, 90.8)
HR [95% CI][c]; p-value[d]	**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[e] (min, max): all patients	61.6 (0.2, 99.4)	59.4 (0.4, 99.1)

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

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

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

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

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

[e] Median follow-up was calculated from the date of randomization.

Data cutoff date = 01 Dec 2016.

Updated OS results, using a cut-off of 01 May 2018 (84.2 months median follow-up for surviving subjects) continue to show an OS advantage 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 versus 44.7% in the Rd arm.

- REVLIMID in combination with bortezomib and dexamethasone in patients who are eligible for stem cell transplantation

The efficacy and safety of Revlimid in combination with bortezomib and dexamethasone (RVd) in this patient group was assessed in two Phase 3 multicentre studies: PETHEMA GEM2012 and IFM 2009.

The PETHEMA GEM2012 study was a Phase 3, randomized, controlled, open-label, multicentre study that compared 2 pre-transplant conditioning regimens (busulfan-melphalan and MEL200) in patients who had received RVd (Revlimid, bortezomib and dexamethasone) as initial therapy. Patients received Revlimid 25 mg/day orally on Days 1-21, bortezomib 1.3 mg/m2 on Days 1, 4, 8, and 11, and dexamethasone 40 mg/day orally on Days 1-4, 9-12 of repeated 28-day cycles. Following initial treatment, patients received either a busulfan-melphalan or MEL200 conditioning regimen (1:1 randomization) and ASCT. Patients also received two additional 4-week cycles of RVd following ASCT. In total 458 patients were enrolled into the study. This study is ongoing and the primary efficacy endpoint of PFS has not been reached yet. The primary efficacy results from the most recent analysis i.e. as of the 31 Mar 2017 data cutoff date, 102 (22.3%) PD or death events have occurred (both arms combined), which is approximately one third of the 294 total events needed for the final analysis of PFS. RVd was given as six 4-week cycles (24 weeks).

The IFM 2009 study was a Phase 3, randomized, controlled, open-label, multicenter study that compared RVd with and without ASCT as initial treatment for patients with previously untreated multiple myeloma who are eligible for transplant. Patients received Revlimid 25 mg/day orally on days 1-14, intravenous bortezomib 1.3 mg/m2 on Days 1, 4, 8, and 11, and dexamethasone 20 mg/day orally on Days 1,2,4,5,8,9,11, and 12 of repeated 21-day cycles. RVd was given as eight 3-week cycles (24 weeks) without immediate ASCT (Arm A) or three 3-week cycles (9 weeks) before ASCT (Arm B). Patients in Arm B also received and two additional 3-week cycles of RVd following ASCT. In total 700 patients were enrolled into the study. Using the EMA censoring rules median PFS was 43.9 months (95%CI 41.1, NE) in the RVd + auto-HSCT arm and 34.8 (95%CI 31.5, 37.7) in the RVd arm. There was a statistically significant 33% reduction of risk of disease progression for subjects treated with RVd + auto-HSCT compared with RVd (HR = 0.67; 95% CI: 0.55, 0.82; p = 0.00010).

A summary of myeloma response rates for the treatment arms utilizing up to 24 weeks of RVd initial treatment (i.e., six 28-day cycles or eight 21-day cycles) for the PETHEMA GEM2012 and IFM 2009 studies, using a cut-off of 31 March 2017 and the 01 December 2016 data respectively, are presented in the table below.

Table 11: An Extract of Efficacy Data from Studies PETHEMA GEM2012 and IFM 2009

	PETHEMA GEM2012 Revlimid + bortezomib + dex [a] (4-week cycles × 6) (N = 458)	**IFM 2009 Revlimid + bortezomib + dex [a] (3-week cycles × 8) (N = 350)**
Myeloma response post initial treatment – n (%)		
Overall response: CR, VGPR, or PR	382 (83.4)	333 (95.1)
≥ VGPR	305 (66.6)	237 (67.7)
CR	153 (33.4)	107 (30.6)
VGPR	152 (33.2)	130 (37.1)
PR	77 (16.8)	96 (27.4)
Myeloma response post transplant – n (%)		

	PETHEMA GEM2012 Revlimid + bortezomib + dex [a] (4-week cycles × 6) (N = 458)	IFM 2009 Revlimid + bortezomib + dex [a] (3-week cycles × 8) (N = 350)
Overall response: CR, VGPR, or PR	372 (81.2)	Not collected
≥ VGPR	344 (75.1)	
CR	202 (44.1)	
VGPR	142 (31.0)	
PR	28 (6.1)	
MRD-negative rate (10^{-4} sensitivity) Post-initial treatment – n (%)		
Overall MRD-negative rate	217 (47.4)	Not collected
≥ VGPR and MRD negative	196 (42.8)	136 (38.9)
MRD-negative rate (10^{-4} sensitivity) Post-transplant - n (%)		
Overall MRD-negative rate	287 (62.7)	Not collected
≥ VGPR and MRD negative	271 (59.2)	

MRD – Minimal Residual Disease: dex = dexamethasone
a Both RVd arms combined.
Data cutoff date = 31 Mar 2017 for the PETHEMA GEM2012 study and 01 Dec 2016 for the IFM 2009 study.

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

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

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

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

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow-up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 9:

Table 9. Summary of overall efficacy data

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

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

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

[b] The 95% CI about the median.

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

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

[e] Exploratory endpoint (PFS2)

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

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

[h] data cut 24 May 2013

- <u>REVLIMID in combination with melphalan and prednisone followed by maintenance therapy in patients who are not eligible for transplant</u>

The safety and efficacy of REVLIMID was assessed in a phase 3 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 REVLIMID in combination with melphalan and prednisone (MPR) with or without REVLIMID maintenance therapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomised in a 1:1:1 ratio to one of 3 treatment arms. Patients were stratified at randomisation by age (≤ 75 vs. > 75 years) and stage (ISS; Stages I and II vs. stage III).

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

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

In an analysis of PFS, PFS2, OS using a cut-off of April 2013 where the median follow up time for all surviving subjects was 62.4 months, the results of the study are presented in Table 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[a] PFS time, months (95% CI)	27.4 (21.3, 35.0)	14.3 (13.2, 15.7)	13.1 (12.0, 14.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.37 (0.27, 0.50); <0.001		
MPR+R vs MPR+p	0.47 (0.35, 0.65); <0.001		
MPR+p vs MPp +p	0.78 (0.60, 1.01); 0.059		
PFS2 (months)[¤]			
Median[a] PFS2 time, months (95% CI)	39.7 (29.2, 48.4)	27.8 (23.1, 33.1)	28.8 (24.3, 33.8)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.70 (0.54, 0.92); 0.009		
MPR+R vs MPR+p	0.77 (0.59, 1.02); 0.065		
MPR+p vs MPp +p	0.92 (0.71, 1.19); 0.051		
Overall survival (months)			
Median[a] OS time, months (95% CI)	55.9 (49.1, 67.5)	51.9 (43.1, 60.6)	53.9 (47.3, 64.2)
HR [95% CI]; p-value			
MPR+R vs MPp+p	0.95 (0.70, 1.29); 0.736		
MPR+R vs MPR+p	0.88 (0.65, 1.20); 0.43		
MPR+p vs MPp +p	1.07 (0.79, 1.45); 0.67		
Follow-up (months)			
Median (min, max): all patients	48.4 (0.8, 73.8)	46.3 (0.5, 71.9)	50.4 (0.5, 73.3)

	MPR+R (N = 152)	MPR+p (N = 153)	MPp +p (N = 154)
Investigator-assessed Myeloma response n (%)			
CR	30 (19.7)	17 (11.1)	9 (5.8)
PR	90 (59.2)	99 (64.7)	75 (48.7)
Stable Disease (SD)	24 (15.8)	31 (20.3)	63 (40.9)
Response Not Evaluable (NE)	8 (5.3)	4 (2.6)	7 (4.5)
Investigator-assessed Duration of response (CR+PR) □ (months)			
Median[a] (95% CI)	26.5 (19.4, 35.8)	12.4 (11.2, 13.9)	12.0 (9.4, 14.5)

CI = confidence interval; CR = complete response; HR = Hazard Rate; M = melphalan; NE = not estimable; OS = overall survival; p = placebo; P = prednisone;
PD = progressive disease; PR = partial response; R = REVLIMID; SD = stable disease; VGPR = very good partial response.
[a] The median is based on the Kaplan-Meier estimate
[¤] PFS2 (an exploratory endpoint) was defined for all patients (ITT) as time from randomisation to start of 3rd line antimyeloma therapy (AMT) or death for all randomised patients

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

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

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

Multiple myeloma with at least one prior therapy
The efficacy and safety of REVLIMID were evaluated in two phase 3 multicentre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of REVLIMID plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received REVLIMID/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 REVLIMID/dexamethasone (len/dex) group took 25 mg of REVLIMID orally once daily on days 1 to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone (placebo/dex) group took 1 placebo capsule on days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both

studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

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

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

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

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 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) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dex (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with len/dex versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dex. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for len/dex and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dex. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the len/dex arm remain significantly higher than in the placebo/dex arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with len/dex versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dex. Despite the fact that 170 out of the 351 patients randomised to placebo/dex received REVLIMID 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 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex(N=351)**	
Time to event			**HR [95% CI], p-value**[a]
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**[b]
Overall response [n, %] Complete response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

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

Myelodysplastic syndromes

The efficacy and safety of REVLIMID were evaluated in patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities, in two main studies: a phase 3, multicentre, randomised, double-blind, placebo-controlled, 3-arm study of two doses of oral REVLIMID (10 mg and 5 mg) versus placebo (MDS-004); and a phase 2, a multicentre, single-arm, open-label study of REVLIMID (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 REVLIMID 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 REVLIMID arms versus the placebo arm (double-blind phase 16 to 52 weeks and open-label up to a total of 156 weeks). Patients who did not have evidence of at least a minor erythroid response after 16 weeks were to be discontinued from treatment. Patients who had evidence of at least a minor erythroid response could continue therapy until erythroid relapse, disease progression or unacceptable toxicity. Patients, who initially received placebo or 5 mg REVLIMID and did not achieve at least a minor erythroid response after 16 weeks of treatment were permitted to switch from placebo to 5 mg REVLIMID or continue REVLIMID treatment at higher dose (5 mg to 10 mg).

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

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

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

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

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

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

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

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

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

The median time to transfusion independence in the REVLIMID 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 REVLIMID-treated subjects. The median increase in haemoglobin (Hgb) from baseline in the 10 mg arm was 6.4 g/dL.

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

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

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

Mantle cell lymphoma

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

Patients who were at least 18 years of age with histologically-proven MCL and CT-measurable disease were enrolled. Patients were required to have received adequate previous treatment with at least one prior combination chemotherapy regimen. Also, patients had to be ineligible for intensive chemotherapy and/or transplant at time of inclusion in the study. Patients were randomised 2:1 to the REVLIMID 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.

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

The baseline demographic were comparable between the REVLIMID 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, intent-to-treat population

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

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

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

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

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

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

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

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

Follicular lymphoma

AUGMENT - CC-5013-NHL-007

The efficacy and safety of REVLIMID in combination with rituximab versus 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 one prior systemic chemotherapy, immunotherapy or chemoimmunotherapy.

REVLIMID 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/m^2 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 REVLIMID 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 REVLIMID in combination with rituximab versus rituximab plus placebo. Further secondary objectives were to compare the efficacy of rituximab plus REVLIMID versus 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% confidence interval [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 follicular lymphoma efficacy data- Study CC-5013-NHL-007

	FL (N = 295)	
	REVLIMID and Rituximab (N = 147)	Placebo and Rituximab (N = 148)
Progression-free survival (PFS) (EMA Censoring Rules)		
Median PFS [a] (95% CI) (months)	39.4 (25.1, NE)	13.8 (11.2, 16.0)
HR [95% CI]	0.40 (0.29, 0.55)[b]	
p-value	< 0.0001[c]	
Objective response[d] (CR +PR), n (%) (IRC, 2007 IWGRC) 95 % CI[f]	118 (80.3) (72.9, 86.4)	82 (55.4) (47.0, 63.6)
Complete response[d], n (%) (IRC, 2007 IWGRC) 95 % CI[f]	51 (34.7) (27.0, 43.0)	29 (19.6) (13.5, 26.9)
Duration of response[d] (median) (months) 95% CI [a]	36.6 (24.9, NE)	15.5 (11.2, 25.0)
Overall Survival[d,e] (OS)		
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]	0.49 (0.28, 0.85)[b]	
Follow-up		
Median duration of follow-up (min, max) (months)	67.81 (0.5, 89.3)	65.72 (0.6, 90.9)

[a] Median estimate from Kaplan-Meier analysis
[b] Hazard ratio and its confidence interval were estimated from unstratified Cox proportional hazard model.

[c] P-value from log-rank test
[d] Secondary and exploratory endpoints are not α-controlled
[e] With a median follow up of 66.14 months, there were 19 deaths in the R^2 arm and 38 deaths in the Control Arm.
[f] Exact confidence interval for binomial distribution.

Follicular lymphoma 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 REVLIMID 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 one 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, REVLIMID 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/m^2 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 (InductionTreatment Period) - Study CC-5013-NHL-008

	All Subjects			FL Subjects		
	Total N=187 [a]	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 [b] ≥ 6 months (95% CI) [c]	**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 [b] ≥ 12 months (95% CI) [c]	**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; DOR = duration of response; FL = follicular lymphoma
[a] Primary Analysis Population for this study is induction efficacy evaluable (IEE) population.
[b] 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.
[c] 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 Revlimid 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
REVLIMID is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

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

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

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

REVLIMID 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 REVLIMID is not metabolised by cytochrome P450 enzymes suggesting that administration of REVLIMID 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 REVLIMID has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or UGT1A1. Therefore, REVLIMID is unlikely to cause any clinically relevant medicinal product interactions when co-administered with substrates of these enzymes.

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

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

REVLIMID 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 REVLIMID exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.

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

Older people

No dedicated clinical studies have been conducted to evaluate pharmacokinetics of REVLIMID in the elderly. Population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and indicate that age does not influence REVLIMID 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 REVLIMID was studied in subjects with renal impairment due to nonmalignant conditions. In this study, two methods were used to classify renal function: the urinary creatinine clearance measured over 24 hours and the creatinine clearance estimated by Cockcroft-Gault formula. The results indicate that as renal function decreases (< 50 mL/min), the total REVLIMID 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 REVLIMID increased from approximately 3.5 hours in subjects with creatinine clearance > 50 mL/min to more than 9 hours in subjects with reduced renal function < 50 mL/min. However, renal impairment did not alter the oral absorption of REVLIMID. The C_{max} was similar between healthy subjects and patients with renal impairment. Approximately 30% of the medicinal product in the body was removed during a single 4-hour dialysis session. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Hepatic impairment

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

Other intrinsic factors

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

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered REVLIMID at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that REVLIMID 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.

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

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with REVLIMID 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 contents
Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Capsule shell
Revlimid 2.5 mg/ 10 mg/ 20 mg hard capsules
Gelatin
Titanium dioxide
FD&C Blue no.2Yellow iron oxide (FDA/E172)

Revlimid 5 mg/ 25 mg hard capsules
Gelatin
Titanium dioxide

Revlimid 7.5 mg hard capsules
Gelatin
Titanium dioxide
Yellow iron oxide (FDA/E172)

Revlimid 15 mg hard capsules
Gelatin
Titanium dioxide
FD&C Blue no.2
Printing ink
Shellac
Dehydrate alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Purified water
Strong ammonia solution
Potassium hydroxide
Black iron oxide
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters containing 7 hard capsules.

Revlimid 2.5 mg/ 5 mg/ 7.5 mg/ 10 mg/ 15 mg/ 20 mg/ 25 mg hard capsules
Pack size of 7 or 21 capsules. Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

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

Healthcare professionals 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).

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

Registration No.
Revlimid 2.5 mg: 33894
Revlimid 5 mg: 31660
Revlimid 7.5 mg: 33896
Revlimid 10 mg: 31661
Revlimid 15 mg: 31662
Revlimid 20 mg: 33965
Revlimid 25 mg: 31663

Manufacturers
Celgene International Sarl, Boudry, Switzerland

Registration Holder
Neopharm Scientific Ltd. P.O.B 7063, Petach Tiqva 4917001

Revised in March 2023 according to MOH guidelines.