MEDICINAL PRODUCT INFORMATION

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Health Care Professionals are asked to report any suspected adverse reactions.

WARNING:

EMBRYO-FETAL TOXICITY,

- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.

- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of Contraception.

HEMATOLOGIC TOXICITY.

REVLIMID can cause significant neutropenia and thrombocytopenia.

For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.

VENOUS THROMBOEMBOLISM

Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving REVLIMID with dex-amethasone. Anti-thrombotic prophylaxis is recommended

1. Name of the medicinal product

REVLIMID 5 mg, 10 mg, 15 mg and 25 mg hard capsules.

2. Qualitative and quantitative composition

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

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

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

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

4. Clinical particulars

4.1 Therapeutic indications

Revlimid in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with untreated multiple myeloma.

Revlimid is indicated for the treatment of adult patients with multiple myeloma as maintenance therapy following autologous stem cell transplantation.

Revlimid in combination with dexamethasone or Revlimid in combination with melphalan and prednisone each followed by Revlimid maintenance therapy, is indicated for the treatment of adult patients with untreated multiple myeloma who are not eligible for transplant.

Revlimid is indicated in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one previous drug treatment.

Revlimid is indicated for the treatment of patients with anaemia requiring transfusions resulting from myelodysplastic syndrome with low or intermediate risk 1 associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

Revlimid is indicated for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL) after prior therapy that included bortezomib and chemotherapy/Rituximab.

4.2 Posology and method of administration

The treatment must be initiated and monitored by an experienced haematologist or oncologist.

MultipleMyeloma

Revlimid in combination with bortezomib and dexamethasone in patients with untreated multiple myeloma

- Initial therapy: Revlimid in combination with bortezomib and dexamethasone

Treatment with Revlimid in combination with bortezomib and dexamethasone must not be started if the absolute neutrophil count (ANC) is < 1.0 x 10^9/L and/or the platelet count is < 50 x 10^9/L.

The recommended initial dose of Revlimid is 25 mg orally once daily, either
a) on days 1-14 of each 21-day treatment cycle or
b) on days 1-21 of each 28-day treatment cycle.

Bortezomib should be given as a subcutaneous injection (1.3 mg/m^2 body surface area) twice weekly on days 1, 4, 8 and 11 of each 21-day or 28-day cycle.

The recommended dexamethasone dose is
a) 20 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11 and 12 or
b) 40 mg orally once daily on days 1 to 4 and 9 to 12 of each cycle.

Up to eight 21-day or six 28-day cycles (24-week initial therapy) are recommended.
Table 1: Recommended dosage regimen for Revlimid in combination with bortezomib and dexamethasone

Up to 8 cycles	Day (of the 21-day cycle)														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-21
Revlimid (25 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	–
Bortezomib (1.3 mg/m^2)	•	–	–	•	–	–	–	•	–	–	•	–	–	–	–
Dexamethasone (20 mg)	•	•	–	•	•	–	–	•	•	–	•	•	–	–	–

or

Up to 6 cycles	Day (of the 28-day cycle)																					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22-28
Revlimid (25 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	–
Bortezomib (1.3 mg/m^2)	•	–	–	•	–	–	–	•	–	–	•	–	–	–	–	–	–	–	–	–	–	–
Dexamethasone (40 mg)	•	•	•	•	–	–	–	–	•	•	•	•	–	–	–	–	–	–	–	–	–	–

- Continuation of treatment in patients not receiving stem cell transplantation: Revlimid in combination with dexamethasone until disease progression

Further treatment with 25 mg Revlimid orally once daily on days 1-21 of the repeated 28-day cycles in combination with dexamethasone. The recommended dexamethasone dose is 40 mg orally once daily on days 1, 8, 15 and 22 of the repeated 28-day cycles. Treatment may be continued until disease progression or intolerance.

- Continuation of treatment: autologous stem cell transplantation

In patients whose treatment is continued with autologous stem cell transplantation, mobilisation of haematopoietic stem cells should take place within the first 4 cycles of initial therapy.

Revlimid in patients following autologous stemcell transplantation
Following autologous stem cell transplantation, initiate Revlimid maintenance therapy after adequate hematologic recovery. Revlimid treatment must not be started if the Absolute Neutrophil Count (ANC) is < 1.0 x 10^9/L, and/or platelet counts are < 75 x 10^9/L.

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

Revlimid in combination with dexamethasone until disease progression in untreated patients who are not

eligible fortransplant

Revlimid treatment must not be started if the ANC is < 1.0 x 10^9/L, and/or platelet counts are < 50 x 10^9/L.

Recommended dose

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

Revlimid in combination with melphalan and prednisone followed by maintenance monotherapy in untreated patients who are not eligible for transplant

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

Recommended dose

The recommended starting dose is Revlimid 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles.

Patients who complete 9 cycles or who are unable to complete the combination therapy due to intolerance are treated with Revlimid alone,10 mg/day orally on days 1-21 of repeated 28-day cycles given until disease progression.

Doseadjustment

The dose of Revlimid or other medicinal products used as part of combination treatment (dexamethasone , melphalan , prednisone, bortezomib) should be adjusted on the basis of clinical findings and laboratory values.

With regard to toxicity-related dose adjustments for other medicinal products used as part of combination treatment, the prescribing information for each respective medicinal product should be consulted.

Haematotoxicity

Recommended dose adjustments during treatment and upon resumption of treatment

For dealing with grade 3 or grade 4 thrombocytopenia or neutropenia, as well as any other grade 3 or grade 4 toxicity rated to be lenalidomide-related, dose adjustments as described below per indication are recommended.

Revlimid in combination with bortezomib and dexamethasone in untreated patients with multiple myeloma

Dose reduction steps

	Lenalidomide
Initial dose	25 mg
Dose level -1	20 mg
Dose level -2	15 mg

Dose level -3	10 mg
Dose level -4	5 mg
Dose level -5	2.5 mg daily or 5 mg every 48 h

Thrombocytopenia

Change in platelet count	Recommended course of action
Drop to < 30 x 10^9/L	Interruption of lenalidomide treatment and weekly monitoring of complete blood count
Recovery to ≥ 50 x 10^9/L	Continuation of lenalidomide at dose level -1
For each subsequent drop below < 30 x 10^9/L	Interruption of lenalidomide treatment
Recovery to ≥ 50 x 10^9/L	Continuation of lenalidomide at the next dose level down. Do not dose below 2.5 mg once daily.

Neutropenia

Change in neutrophil count	Recommended course of action [a]
First drop to < 0.5 x 10^9/L or febrile neutropenia (fever ≥ 38°C; < 1 x 10^9/L)	Interruption of lenalidomide treatment and weekly monitoring of complete blood count
Recovery to ≥ 1 x 10^9/L	Continuation of lenalidomide at dose level -1
For each subsequent drop below < 0.5 x 10^9/L or febrile neutropenia	Interruption of lenalidomide treatment

Recovery to ≥ 1 x 10^9/L	Continuation of lenalidomide at the next dose level down. Do not dose below 2.5 mg once daily.

[a] If, at any dose level, neutropenia occurs as the only toxicity, granulocyte colony stimulating factor (G-CSF) is given at the discretion of the physician, while maintaining the lenalidomide dose level.

Revlimid in patients following autologous stem cell transplantation

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

Dosereductionsteps

	Starting dose (10 mg)	If dose increased (15mg)[a]
Dose level -1	5 mg once daily continuously	10 mg once daily continuously
Dose level -2	5 mg once daily on days 1-21 of 28-daycycles	5 mg once daily continuously
Dose level -3	Not applicable	5 mg once daily on days 1-21 of 28-day cycles
	Do not dose below 5 mg once daily on days 1-21 of 28-day cycles	

[a] After three 28-day cycles of continuous Revlimid maintenance, the dose can be increased to 15 mg orally once daily if tolerated.

Thrombocytopenia

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment and follow complete blood count weekly
Return to ≥ 30 x 10^9/L	Resume lenalidomide at dose level -1
For each subsequent drop below < 30 x 10^9/L	Interrupt lenalidomide treatment

Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level

Neutropenia

When neutrophils	Recommended course[a]
Fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment and follow complete blood count weekly
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at dose level -1
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level

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

Revlimid in combination with dexamethasone in untreated patients who are not eligible for transplant

Dose reduction steps

	Lenalidomide	Dexamethasone
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 daily or 5 mg every 48h	N/A

Thrombocytopenia

When platelets	Recommended course
Fall to < 25 x 10^9/l	Stop lenalidomide dosing for remainder of cycle[a]
Return to ≥ 50 x 10^9/l	Resume lenalidomide at 5 mg less than the previous dose. After 5 mg dose, resume lenalidomide at 2.5 daily or 5 mg every 48 hours. Do not dose below 2.5 mg daily or 5 mg 48 hours.

[a] If Dose Limiting Toxicity (DLT) occurs on > Day15 of a cycle, lenalidomide dosing will be interrupted for at least the remainder of the current 28-day cycle.

Neutropenia

Whenneutrophils	Recommendedcourse
First fall to < 0.5 x 10^9/L or febrile neutropenia (fever ≥ 38°C; < 1 x 10^9/L)	Interrupt lenalidomide treatment
Return to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0,5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0,5 x 10^9/l	Resume lenalidomide at next lower dose level once daily.

[a] *If, at any dose level, neutropenia occurs as the only toxicity, granulocyte colony stimulating factor (G-CSF) is given at the discretion of the physician, while maintaining the lenalidomide dose level.*

If the dose of lenalidomide was reduced for a hematologic DLT, the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) at the discretion of the treating physician if continued lenalidomide / dexamethasone therapy resulted in improved bone marrow function (no DLT for at least 2 consecutive cycles and an ANC ≥1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

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

Dose reduction steps

	Lenalidomide	Melphalan	Prednisone
Starting dose	10 mg[a]	0.18 mg/kg	2 mg/kg
Dose level -1	7.5 mg daily or 15 mg every48h	0.14 mg/kg	1 mg/kg
Doselevel-2	5mg	0.10mg/kg	0.5mg/kg
Dose level -3	2.5 mg daily or 15 mg every 48 h	N/A	0.25 mg/kg

Thrombocytopenia

When platelets	Recommended course
First fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l	Resume lenalidomide and melphalan at Doselevel-1
For each subsequent drop below	30 x 10^9/l

Return to ≥ 30 x 10^9/l	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose level -2 or -3) once daily.

,

Neutropenia	
When platelets	Recommended course
First fall to < 0,5 x 10^9/l[a]	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at Starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose level -1 once daily
For each subsequent drop below < 0,5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0,5 x 10^9/l	Resume lenalidomide at next lower dose level once daily.

[a] *If, at any dose level, neutropenia occurs as the only toxicity, granulocyte colony stimulating factor (G-CSF) is given at the discretion of the physician, while maintaining the lenalidomide dose level.*

Revlimid in combination with dexamethasone in patients with multiple myeloma who received at least one prior therapy

The recommended starting dose is 25 mg Revlimid orally once a day on days 1–21 of the repeating 28-day treatment cycles. The recommended dose of dexamethasone is 40 mg orally once a day on days 1–4, 9–12 and 17–20 of each 28-day cycle during the first 4 treatment cycles and then 40 mg once daily on days 1–4 of each cycle. Treatment should be continued until disease progression or until the occurrence of unacceptable toxicity.

Doseadjustment

Recommended dose adjustments during multiple myeloma treatment and restart of treatment

Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

• *Dose reduction steps*

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

Platelet counts

Thrombocytopenia When platelets	Recommended Course
First fall to < 30 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/l	Resume lenalidomide at Dose Level 1
For each subsequent drop below 30 x 109/l	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level 2 or 3) once daily. Do not dose below 5 mg once daily.

Absolute Neutrophil counts (ANC)

Neutropenia When neutrophils	Recommended Course
First fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	Resume lenalidomide at Starting Dose once daily
Return to ≥ 0.5 x 10^9/l when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level 1, 2 or 3) once daily. Do not dose below 5 mg once daily.

Myelodysplastic syndrome

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) < 0.5 x 10^9/l and/or platelet counts < 25 x 10^9/l.

Recommendeddose

The recommended starting dose of lenalidomide is 10 mg orally once daily on days 1-21 of repeated 28-day cycles. Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Recommendeddoseadjustmentsduringtreatmentandrestartoftreatment

Dose adjustments, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- *Dose reduction steps*

Starting Dose	10 mg once daily on days 1-21 every 28 days
Dose Level -1	5.0 mg once daily on days 1-28 every 28 days
Dose Level -2	2.5 mg once daily on days 1-28 every 28 days
Dose Level -3	2.5 mg every other day 1-28 every 28 days

For patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia:

- *Thrombocytopenia*

When platelets	Recommended Course
Fall to < 25 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 25 x 10^9/l - < 50 x 10^9/l on at least 2 occasions for ≥ 7 days or when the platelet count recovers to ≥ 50 x 10^9/l at any time	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 0.5 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	Resume lenalidomide at next lower dose level (Dose Level -1, -2 or -3)

Relapsed or refractory mantle cell lymphoma

The recommended starting dose of Revlimid is 25 mg/day orally on days 1-21 of repeated 28-day treatment cycles. Treatment should be continued until disease progression or unacceptable toxicity.

Recommended dose adjustments during treatment and restart of treatment

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

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

- *Neutropenia*

When neutrophils	Recommended Course
Fall to < 1 x 10^9/L for at least 7 days or Falls to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or Fallsto<0.5x10^9/L	Interrupt lenalidomide treatment and conduct the CBC at least every 7 days
Return to ≥ 1 x 10^9/L	Resume lenalidomide at next lower dose level (Dose Level -1)
For each subsequent drop below 1 x 10^9/L for at least 7 days or drop to < 1 x 10^9/L with associated fever (body temperature ≥ 38.5°C) or drop to < 0.5 x10^9/L	Interrupt lenalidomide treatment

When neutrophils	Recommended Course
Returns to ≥1 x 10^9/L	Resume Lenalidomide at next lower dose level (Dose Level -2, -3, -4, -5). Do not dose below DoseLevel-5

Dose adjustment for other reasons

If a non-scaly grade 3 rash (with blistering), grade 3 neuropathy or grade 2 allergic reaction occurs, the treatment must be suspended. It can be resumed at the next dose down after appropriate regression to ≤ grade 1.

If a scaly rash (with blistering), a grade 4 non-scaly rash (with blistering), grade 4 neuropathy or ≥ grade 3 allergic reaction occurs, Revlimid must be stopped.

If constipation (≥ grade 3) occurs, the treatment must be suspended and treatment of the constipation initiated. The treatment with Revlimid can be resumed at the next dose down after regression of the constipation to ≤ grade 2.

If a venous thrombosis/embolism (≥ grade 3) occurs, the treatment must be suspended and anticoagulant treatment initiated. Resumption of the therapy is at the physician's discretion (keeping the same dose).

Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, if Stevens-Johson syndrome (SJS) toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS) is suspected, and should not be resumed following discontinuation for these reactions.

Other grade 3/4 toxicities

For other grade 3/4 toxicities judged to be related to Revlimid, the treatment should be stopped and restarted at the next dose down at the physician's discretion once the toxicity has resolved to ≤ grade 2.

Method of Administration

Revlimid capsules should be taken at the same time each day, with or without meals, but with water. The capsules should not be opened or chewed. Hands should be washed immediately after contact with the capsules. Care must be taken to ensure that the powder contained in the capsules is not inhaled and does not come into contact with the skin or mucous membranes (e.g. in the case of damage to a capsule). If skin contact occurs, the site should be washed with soap and water. If the product comes into contact with the eyes, they should be rinsed with water.

If less than 12 hours have elapsed since a dose of Revlimid has been missed, the dose can be taken. 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. Do not take 2 doses at the same time.

Specialdosageinstructions

Paediatricpatients:

Safety and effectiveness in paediatric patients below the age of 18 have not been established. For that reason, Revlimid should not be used in this age group.

ElderlyPatients:

Dose adjustments are not necessary. Since elderly patients are more likely to have reduced renal function, renal function should be monitored on a regular basis in these patients.

REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age. REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Patients with untreated multiple myeloma who are not eligible for transplant

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

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

Patients with renal impairment

Lenalidomide is substantially excreted by the kidney, therefore 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 or myelodysplastic syndromes. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

- *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[2,3] 15 mg every other day
End stage renal impairment (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.

[3] The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment.

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

In the treatment of patients with MCL, an effect of renal function on the plasma concentrations of Revlimid, the active substance, may be expected to be similar to the effect observed in patients with MM and of an SMD. A reduction in the corresponding dose should be considered in patients with MCL who have renal impairment. It should be noted that the initial dose of 10 mg should not be exceeded in patients with a creatinine clearance between 30 and 60 ml / min.

- *Myelodysplastic syndromes*

Renal Function (CLcr)	**Dose Adjustment**	
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	Starting dose	5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg once daily (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg once every other day (days 1-28 of repeated 28-day cycles)

Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

End stage renal impairment (CLcr < 30 ml/min, requiring dialysis) On dialysis days, the dose should be administered following dialysis.	Starting dose	2.5 mg once daily (days 1-21 of repeated 28-day cycles)
	Dose level -1	2.5 mg every other day (days 1-28 of repeated 28-day cycles)
	Dose level -2	2.5 mg twice a week (days 1-28 of repeated 28-day cycles)

- *Mantle cell lymphoma*

Renal function (CLcr)	**Dose adjustment** (Days 1-21 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.

Patientswithliverfunctiondisorders:

Revlimid has not been investigated in patients with disorders of liver function and there are no special dosage recommendations.

CessationoftreatmentbecauseofinsufficientefficacyinMDSpatients

If at least a slight response, i.e. at least a 50% improvement is not seen 16 weeks after the start of the Revlimid treatment, cessation of treatment due to lack of efficacy is recommended.

4.3 Contraindications

Pregnancy

Women of childbearing potential except when all of the conditions of the i-SECURE (Pregnancy Prevention Programme) have been fulfilled (see “Warnings and Precautions“).

Hypersensitivity to lenalidomide or any of the excipients.

4.4 Special warnings and precautions

Pregnancy Prevention Programme

Programme in female patients

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless it has been proven that the patient cannot become pregnant.

Criteria for clarification of the potential for pregnancy

A female patient or the female partner of a male patient is classified as having childbearing potential unless she fulfils at least one of the following conditions:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 years*
- Premature ovarian failure confirmed by a gynaecologist
- Female that has not begun menstruation
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner’s syndrome, uterine agenesis

* Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling

Lenalidomide is contraindicated in women of childbearing potential unless all of the following conditions are met:

- The patient understands the expected teratogenic risk to the unborn child.

- She understands the need for using two forms of effective contraception without interruption for 4 weeks prior to the start of treatment, throughout the entire treatment including interruptions to treatment, and for 4 weeks after the end of treatment.

- Even if a female patient of childbearing potential is amenorrhoeic, she must follow all of the recommendations for effective contraception.

- she should be capable of adhering to effective contraceptive measures.

- She is informed and understands the consequences of a pregnancy and the necessity of seeking medical advice promptly if a pregnancy is suspected.

- She understands the need for pregnancy tests every 4 weeks (unless confirmed tubal sterilization) and is willing to have them done.

- She has confirmed that she understands the risks and the necessary safety precautions associated with taking lenalidomide.

The prescribing physician must ensure in women of childbearing potential that:

- The patient fulfils the above conditions.

- The patient complies with the conditions for contraception, including confirmation of an adequate level of understanding.

- The patient has used two forms of effective contraceptive measures for at least 4 weeks before the start of treatment and will continue to use two forms of effective contraceptive measures for the entire treatment period, including treatment interruptions, and for at least 4 weeks after completing treatment.

- There is a negative result of a pregnancy test prior to the start of treatment.

Contraception

Women of childbearing potential must use two forms of effective contraceptive methods for 4 weeks before the start of treatment, throughout treatment, including treatment interruptions, and for 4 weeks after completing treatment. If effective contraceptive methods have not been used previously, the patient must be referred to a medical counselling service, where she will receive comprehensive counselling regarding effective contraceptive methods.

The following can be regarded as effective contraceptive methods:

- Highly effective methods:

  - Intra Uterine Device (IUD)

  - Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills e.g. desogesterol)

  - Tubal ligation

  - Partner's vasectomy

- Effective methods:

  - Male condom

- Diaphragm

  - Cervical cap

Because of the increased risk of venous thromboembolism on lenalidomide, combined oral contraceptives are not recommended. If a patient is already using combined oral contraceptives, a change to another contraceptive method should be considered. The risk of venous thromboembolism persists for 4-6 weeks after cessation of treatment with combined oral contraceptives. If other methods cannot be

used, thrombosis prophylaxis should be considered during the continued use of combined oral contraceptives. The patient should be properly informed about the risk of venous thromboembolism.

Intrauterine devices have an increased risk of infections during insertion and can lead to irregular vaginal bleeding. Therefore these methods are not recommended.

Pregnancy tests

Pregnancy tests with a sensitivity of at least 25 mIU/ml hCG must be performed in women of childbearing potential.

Any case of a patient with a positive pregnancy test must be reported immediately as per the requirements of the Pregnancy Prevention Program.

- *Before the start of treatment*

A pregnancy test must be performed during the consultation at which lenalidomide is prescribed, or within seven days prior to the appointment with the prescribing physician, after the patient has used effective contraception for at least 4 weeks. The test is intended to ensure that the patient is not pregnant before starting treatment with lenalidomide.

Before starting treatment in patients requiring immediate treatment:
A quantitative determination of serum hCH should be made immediately. After 7 days of applying an effective method of contraception, combined with the use of condoms, the test must be repeated. If both tests confirm that the patient is not pregnant, treatment can be started."

- *During and after completing treatment*

A pregnancy test must be repeated every 4 weeks (unless confirmed tubal sterilization), including 4 weeks after the end of treatment. These pregnancy tests should be done during the consultations at which lenalidomide is prescribed, or within seven days before the consultation.

Pregnancy tests, the prescribing and dispensing of lenalidomide should ideally occur on the same day. Lenalidomide must be dispensed within a maximum of 7 days after the last pregnancy test.

Programme formalepatients

For male patients taking Revlimid, clinical data have demonstrated the presence of this active sub- stance in the semen. Therefore, male patients with partners of childbearing potential not established on suitable contraception should use condoms during sexual intercourse during the duration of treatment with Revlimid, during dose interruption and for at least 1 week after the end of the treatment (even if the male patient has undergone a vasectomy). Men who take Revlimid must fulfil the following condi- tions:

- They must understand the expected teratogenic risk if they are having sexual intercourse with a woman of childbearing potential.

- They must understand and agree to use a condom when they have sexual intercourse with a woman of childbearing potential for the entire duration of treatment, including treatment interruptions, and for at least 1 week after the end of treatment treatment (even if the male patient has undergone a vasec- tomy).

The prescribing physician must ensure that male patients understand the need to use a condom when they have sexual intercourse with a woman of childbearing potential for the entire duration of treatment, including treatment interruptions, and for 1 week after completing treatment, and agree to do so.

Male patients may not donate semen or sperm during treatment with Revlimid and for 1 week following the discontinuation of Revlimid.

Prescribing and dispensing restrictions

For women of childbearing potential, prescriptions of Revlimid should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription.

For all other patients, prescriptions of Revlimid should be limited to 12 weeks and continuation of treatment requires a new prescription.

Additional Precautions

Patients must be instructed never to give this medicinal product to another person and to return unused

capsules to their pharmacist after the end of therapy. Patients must be instructed to not donate blood whilst taking Revlimid and for 4 weeks following the discontinuation of Revlimid.

Information material

In order to assist patients in preventing contact of unborn children with Revlimid, the marketing authorisation holder shall supply the following information material to health care professionals and patients:

- Medicinal product data sheet
- Information for health care professionals about the Pregnancy Prevention Programme for Revlimid
- Pregnancy prevention methods
- Patient brochure about the Pregnancy Prevention Program

Other Warnings and Precautions

Neutropenia and thrombocytopenia

Neutropenia and thrombocytopenia are among the most important dose-limiting toxicities of lenalidomide. For that reason, a complete blood count with differential blood count, platelet count, haemoglobin concentration and haematocrit should be performed.

In patients with untreated multiple myeloma who are eligible for transplant and who are taking Revlimid in combination with bortezomib and dexamethasone, a complete blood count should be assessed every 7 days (once weekly) during the first treatment cycle and then prior to the start of each subsequent cycle. Continuation of treatment with Revlimid in combination with dexamethasone requires monthly monitoring (every 4 weeks).

In patients with multiple myeloma following autologous stem cell transplantation who are taking Revlimid, a complete blood count should be assessed every 7 days (once weekly) in the first two 28-day cycles, every 2 weeks (day 1 and day 15) in the third 28-day cycle and every 28 days (4 weeks) thereafter.

In MM-patients following autologous stem cell transplantation, who take Revlimid, complete blood count should be assessed every 7 days (once a week) for the first two 28-day cycles, every 2 weeks (Day 1 and Day 15) during the third 28-day cycle, and then once every 28 days (4 weeks) thereafter. A treatment interruption and/or dose reductions may be required (see “Dosage/Administration”). Patients with neutropenia should be monitored for signs of infection. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxis, especially with use of concomitant medication that may increase risk of bleeding. Appropriate management should be instituted if such toxicity is observed.

In MM-patients with untreated multiple myeloma who are not eligible for transplant, who take Revlimid in combination with melphalan and prednisone, complete blood count should be assessed every 7 days (1 week) for the 1st cycle (28-days), every 14 days (2 weeks) until 9 cycles and every 28 days (4 weeks) thereafter.

In MM-patients with untreated multiple myeloma who are not eligible for transplant, who take Revlimid in combination with dexamethasone complete blood count should be assessed every 7 days (weekly) for the first 2 cycles, day 1 and day 15 of cycle 3, and every 28 days (4 weeks) thereafter.

In patients with multiple myeloma who have received at least one previous treatment and who are taking Revlimid in combination with dexamethasone, the complete blood count should be monitored every 14 days (2 weeks) during the first 12 weeks of therapy and once monthly thereafter.

In patients taking Revlimid for MDS with deletion 5q abnormality, the complete blood count should be monitored once weekly in the first 8 weeks of therapy and once monthly thereafter.

Patients taking Revlimid for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. A dose interruption and or dose reduction may become necessary (see Dosage/Administration). Patients should be asked to inform the treating physician if there is any fever or bleeding, including petechiae and nosebleeds.

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. 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.

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

Patients with a baseline age > 75 years, ISS Stage III, ECOG PS ≥ 2, or CrCl < 60 mL/min have demon- strated a higher rate of intolerance (Grade 3 or 4 AEs, SAEs, discontinuation due to AEs) when lenalid- omide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalid- omide in combination, with consideration to age and other comorbidities.

Disorders of thyroid function

Both hypothyroidism and hyperthyroidism have reported in patients treated with lenalidomide (see “Un- desirable Effects”). Optimal control of co-morbid conditions that can affect thyroid function is recom- mended before start of Revlimid treatment. Baseline and ongoing monitoring of thyroid function is rec- ommended.

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including previous thrombosis – should be closely monitored, and measures should be taken to minimise all modifiable risk factors (eg. smoking, hyper- tension, and hyperlipidaemia).

The risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) is increased. Therefore, there is a need to be especially alert to the symptoms of thrombosis or thromboembolism. Patients must be instructed to seek medical help if symptoms such as shortness of breath, cough, chest pain or pain and/or swelling of the arms and legs occur. Treatment with erythropoietic agents and hormone replace- ment therapy can increase the risk of thromboembolism and thus should not be given.

Venous and arterial thromboembolic events

There is an increased risk of venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism), in multiple myeloma patients treated with lenalidomide in combination with dexamethsone or other chemotherapy. The risk of VTE is lower in MDS and MCL patients treated with lenalidomide monotherapy

There is an increased risk of arterial thromboembolic events (predominantlymyocardial infarction and cerebrovascular events) in patients treated with lenalidomide and dexamethasone, and to a lesser ex- tent with melphalan and prednisone.

Consequently, patients with known risk factors for thromboembolism – including previous thrombosis – should be closely monitored. Measures should be taken to minimise all modifiable risk factors (e.g. smoking cessation, control of hypertension and hyperlipidaemia).

Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. A haemoglobin concentration above 11 g/dL should lead to discontinuation of erythropoietic agents.

Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision whether to take antithrombotic prophylactic measures should be made

after careful assessment for each patient individually.

If a thromboembolic event occurs, treatment with lenalidomide must be discontinued and standard anticoagulation therapy started. Once the patient's condition has stabilised, treatment with lenalidomide may be resumed if required, with continuation of the anticoagulation.

Cardiac electrophysiology Prolongation of the QTc interval has been observed on the ECG during treatment with lenalidomide. Concurrent treatment with drugs prolonging QT interval and treatment of patients with long QT syndrome should take place only with great caution and regular ECG monitoring.

Allergic Reactions and Serious Skin Reactions
Angioedema and severe dermatological reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These can be fatal. Revlimid interruption or discontinuation should be considered for Grade 2-3 skin rash. Revlimid must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash. if SJS, TEN or DRESS is suspected and should not be resumed following discontinuation of the drug or these reactions. Patients with severe grade 4 rash associated with thalidomide treatment should not receive Revlimid.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) may occur including in patients with lymphoma. The patients at risk of tumor lysis syndrome are those with a high tumor burden prior to the start of treatment. These patients should be closely monitored, especially during the first cycle or dose-escalation and appropriate pre- cautions taken.

Tumor Flare Reaction

Careful monitoring and evaluation for tumor flare reaction (TFR) is recommended. Tumor flare may mimic progression of disease (PD). In the pivotal MCL-001 study, approximately 10% of subjects expe- rienced TFR; all reports were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. Lenalidomide may be continued in patients with Grade 1 and
2 TFR without interruption or modification, at the physician's discretion. Patients in study MCL-001 that experienced Grade 1 and 2 TFR were treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. The decision to take therapeutic measures for TFR should be made after careful clinical assessment of the individual patient. In patients with Grade 3 or 4 TFR, withhold treatment with lenalidomide until TFR resolves to ≤ Grade
1 and patients may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

Lactose intolerance

Revlimid capsules contain lactose. Patients with a rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this drug.

Cases of transiently abnormal liver function tests (mainly transaminases) have been reported in patients treated with Revlimid. Treatment with Revlimid should be suspended. Treatment with Revlimid can be continued once the levels have returned to baseline. Successful re-challenge without recurrence of elevated liver enzymes has been reported in some patients.

Combination therapy

For information on other medicinal products used in combination with lenalidomide, reference should be made to the respective product prescribing information.

Hepatic Disorders

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hep- atitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug- induced

hepatotoxicity remain unknown although, in some cases, preexisting viral liver disease, ele- vated 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. Cases of transiently abnormal liver function tests (mainly transaminases) have been reported in patients treated with Revlimid. Treatment with Revlimid should be suspended. Treatment with Revlimid can be continued once the levels have returned to baseline. Successful re-challenge without recurrence of elevated liver enzymes has been reported in some patients.

Lenalidomide is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological side effects or hepa- totoxicity. Monitoring of liver function is recommended, particularly when there is a history of or concur- rent viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction. Cases of transiently abnormal liver function tests (mainly transaminases) have been reported in patients treated with Revlimid. Treatment with Revlimid can be continued once the levels have returned to baseline. Successful re-challenge without recurrence of elevated liver enzymes has been reported in some patients.

Concomitant treatment with medicinal products that prolong the QT interval and treatment in patients with long QT syndrome should proceed only with extreme caution and regular ECG monitoring (see “Properties/Effects”).

Second Primary Malignancies

Based on a low number of cases, a numerical imbalance was observed in clinical trials in previously treated multiple myeloma patients with lenalidomide/dexamethasone compared with controls compris- ing mainly of basal cell and squamous cell skin cancers.

In clinical trials in newly diagnosed multiple myeloma patients, an increase of hematologicsecond pri- mary malignancies including AML and MDS has been observed predominantly in patients receiving lenalidomide in combination with melphalan (frequency of 5.3%) or immediately following high dose melphalan and ASCT (frequency of up to 5.2%). The frequency of AML and MDS cases in the Revlimid / dexamethasone arms was observed to be 0.4%.

Cases of B-cell malignancies (including Hodgkin’s Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting.

An increase in solid SPMs was observed in patients who received lenalidomide immediately following high-dose intravenous melphalan (HDM) and ASCT (frequency of 7.7%).

In patients with newly diagnosed multiple myeloma receiving lenalidomide in combination with bortezomib and dexamethasone, the frequency of haematological SPMs was 0.0% to 0.8% and the frequency of solid SPMs was 0.4% to 4.5%.

Take into account both the benefit achieved with lenalidomide and the risk of second primary malignan- cies before initiating treatment with lenalidomide. Carefully evaluate patients before and during treat- ment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

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. 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.

Patients with a baseline age > 75 years, ISS Stage III, ECOG PS ≥ 2, or CrCl < 60 mL/min have demonstrated

a higher rate of intolerance (Grade 3 or 4 AEs, SAEs, discontinuation due to AEs) when lenalidomide is given in combination. Patients should be carefully assessed for their ability to tolerate lenalidomide in combination, with consideration to age and other comorbidities.

Infections

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

Early death in MCL patients

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

Rejection reactions following organ transplantation

Cases of organ transplant rejection have been reported in post-marketing experience with the use of Revlimid, some of which were fatal. In the majority of cases, the rejection reaction occurred within the first 2 months of starting therapy with Revlimid. Possible factors contributing to organ transplant rejection in the reported cases are underlying disease (e.g. amyloidosis), concurrent infections and recent discontinuation or reduction of immunosuppressive therapy. The incidence rate of rejection reactions in organ transplants cannot be reliably estimated due to the limitation of post-marketing safety data. As a rule, Revlimid was permanently discontinued at the onset of the rejection reaction. Prior to initiation of therapy with Revlimid, the benefit of treatment with Revlimid versus the risk of possible organ transplant rejection should be considered in organ transplant recipients.

Immunosuppressive effects

Lenalidomide has powerful immunosuppressive effects. Therefore, caution should be exercised when coadministered with other immunomodulatory agents. The effectiveness of some vaccines may be affected. Because of the risk of infection, the administration of live vaccines should be avoided during treatment with lenalidomide.

4.5 Interactions with other medicinal products and other forms of interaction

Since lenalidomide is not metabolised via the phase I enzyme system and its plasma protein binding is low, interactions via the cytochrome P450 system and via protein binding are unlikely.

Since lenalidomide is eliminated by active tubular secretion, interactions with other drugs that are eliminated by active tubular secretion are possible. There is little experience in the case of elevated uric acid levels.

Lenalidomide (10 mg) had no effect on the pharmacokinetics of R- and S-warfarin administered con- currently as a single dose. A single dose of 25 mg of warfarin had no effect on the pharmacokinetics of lenalidomide administered concurrently. However, it is not known whether there is an interaction during clinical use. Close monitoring of the warfarin concentration is therefore advisable during treatment.

Treatment with coumarins is not recommended due to the high risk of thrombocytopenia.

Dexamethasone (40 mg/day) had no effect on the pharmacokinetics of Revlimid.

Concomitant administration with lenalidomide 10 mg/day 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 therapeutic situation (higher lenalidomide doses and concomitant treat- ment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during le- nalidomide treatment. Co-administration of multiple doses of the P-gp inhibitor quinidine (600 mg, twice daily) has no effect on the pharmacokinetic (PK) of lenalidomide (25 mg).

Co-administration of lenalidomide (25 mg) and the P-gp inhibitor/substrate temsirolimus (25 mg) does not alter the PK of either drug.

Agents that stimulate erythropoiesis or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should only be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.

4.6 Fertility, pregnancy and lactation

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

Womenofchildbearingpotential/Contraceptioninmalesandfemales

Women of childbearing potential should use two effective methods of contraception. If pregnancy oc- curs in a woman treated with lenalidomide, treatment must be stopped and the patient should be re- ferred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Pregnancy

Pregnancy category X

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Breast-feeding

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

Fertility

A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg

4.7 Effects on ability to drive and use machines

No studies have been conducted on the effects on the ability to drive and operate machinery. Adverse effects such as fatigue, light-headedness, somnolence and blurred vision may occur on Revlimid. Therefore, caution is advised when patients drive or operate machinery.

4.8 Undesirable effects

Multiple myeloma

Patients with untreated multiple myeloma who are eligible for transplant and who received lenalidomide in combination with bortezomib and dexamethasone

In the studies PETHEMA GEM2012 (pooled arm A and B (RVd), n=458) and IFM 2009 (Arm A (RVd), n=356), the following serious adverse reaction was observed most frequently (≥ 5%) with lenalidomide in combination with bortezomib and dexamethasone:

- Pneumonia (5.9%) in PETHEMA GEM2012.

In the PETHEMA GEM2012 study, the adverse reactions observed most frequently with lenalidomide in combination with subcutaneous bortezomib and dexamethasone were: peripheral neuropathy (35.2%), neutropenia (31.9%) and thrombocytopenia (25.3%).

In the IFM 2009 study, the adverse reactions observed most frequently with lenalidomide in combination with intravenous bortezomib and dexamethasone were: peripheral neuropathy (54.8%) and lymphopenia (52.2%).

Patients with multiple myeloma who received lenalidomide following autologous stem cell transplantation

In two double blind, placebo-controlled, 2-arm phase III studies (IFM 2005-02 and CALGB 100104) 517 patients received lenalidomide and 501 patients received placebo. The adverse reactions from CALGB 100104 included not only events from the maintenance treatment period but also events reported post-HDM/ASCT. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

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

- Pneumonias (10.6%; combined term)
- Lung infection (9.4%)

The adverse reactions observed more frequently with lenalidomide maintenance than placebo in either of the 2 clinical studies were neutropenia (79.0%), thrombocytopenia (72.3%), diarrhoea (54.5%), bronchitis (47.4%), nasopharyngitis (34.8%), muscle spasms (33.4%), rash (31.7%), leukopenia (31.7%), asthenia (29.7%), cough (27.3%), upper respiratory tract infection (26.8%), fatigue (22.8%), gastroenteritis (22.5%), anaemia (21.0%) and pyrexia (20.5%).

Patients with untreated multiple myeloma who received lenalidomide in combination with low dose dexamethasone

In an open-label, 3 arm phase III study 535 patients received the lenalidomide/low dose dexamethasone combination until progressive disease (Rd), 541 patients receive the lenalidomide/low dose dexamethasone combination up to eighteen 28-day cycles (Rd18) and 547 patients the melphalan, prednisone and thalidomide combination.

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

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

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

Patients with untreated multiple myeloma who received lenalidomide in combination with melphalan and prednisone

In a double-blind, placebo-controlled, 3-arm phase III study the safety and efficacy of combination therapy for melphalan, prednisone and lenalidomide (MPR) followed by lenalidomide maintenance monotherapy was evaluated. 152 Patient received oral MPR induction combination therapy followed by lenalidomide maintenance therapy (MPR+R), 153 patients received oral MPR induction combination therapy followed by placebo maintenance treatment (MPR+p) and 154 patient oral MPp (MP + placebo) induction combination therapy followed by placebo maintenance treatment (MPp+p).

The serious adverse reactions observed more frequently (≥ 5%) with melphalan prednisone, and lenalidomide followed by lenalidomide maintenance (MPR+R) or melphalan prednisone, and lenalidomide followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were:

- Febrile neutropenia (6.0%)
- Anaemia (5.3%)

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

Patients with multiple myeloma who received at least on prior therapy

In placebo-controlled phase III studies 353 patients received the lenalidomide/dexamethasone combination and 350 patients the placebo/dexamethasone combination. At least one side effect was observed in 325 patients (92%) in the lenalidomide/dexamethasone group, compared with 288 patients (82%) in the placebo/dexamethasone group.

The most serious undesirable effects observed were venous thromboembolism (deep vein thrombosis, pulmonary embolism) and grade 4 neutropenia.

The most frequently observed undesirable effects in the lenalidomide/dexamethasone group were neutropenia (39.4%; grade 4: 5.1%), thrombocytopenia (18.4%, grades 3-4: 9.9%), fatigue (27.2%), constipation (23.5%), muscle cramps (20.1%), asthenia (17.6%), anaemia (17.0%), diarrhoea (14.2%) and rash (10.2%), insomnia (26.7%) and muscle weakness (10.1%). The occurrence of neutropenia and thrombocytopenia was mainly dose-dependent, and these conditions were successfully treated with dose reduction.

Myelodysplasticsyndrome

In a placebo-controlled Phase III study 69 patients received 10 mg lenalidomide once daily and 67 patients received placebo.

The most serious undesirable effects observed were venous thromboembolisms (deep vein thrombosis, pulmonary embolism), grades 3-4 neutropenia, febrile neutropenia and grades 3-4 thrombocytopenia.

The most frequently observed undesirable effects in the lenalidomide group were neutropenia (76.8%; grades 3-4: 75.4%), thrombocytopenia (49.3%; grades 3-4: 40.6%), diarrhoea (37.7%), pruritus (27.5%), nausea (20.3%), fatigue (18.8%), constipation (17.4%), muscle spasm (17.4%), pyrexia (15.9%), nasopharyngitis (14.5%), bronchitis (14.5%) and headache (14.5%). The occurrence of neu- tropenia and thrombocytopenia was mainly dose-dependent and these conditions were successfully treated with dose reduction.

Mantle cell lymphoma

In the pivotal MCL study, a total of 134 patients received at least 1 dose of Revlimid.

The most common type of serious adverse events was infection. Of the serious infections, pneumonia was the most frequently reported.

The most frequently observed undesirable effects were pneumonia (14.2%; Grade 3-4: 9%), Upper respiratory tract infection (12.7%), neutropenia (48.5%; Grade 3-4: 43.3%), thrombocytopenia (35.8%; Grade 3-4: 27.6%), anaemia (30.6%; Grade 3-4: 11.2%), leucopenia (14.9%; Grade 3-4: 6.7%), decreased appetite (14.2%), hypokalaemia (12.7%; Grade 3-4: 2.2%), weight decreased (12.7%), cough (28.4%), dyspnoea (17.9%; Grade 3-4: 6%), diarrhoea (31.3%; Grade 3-4: 6%), nausea (29.9%), constipation (15.7%), vomiting (11.9%), rash (22.4%; Grade 3-4: 1.5%), pruritus (17.2%), back pain (13.4%; Grade 3-4: 1.5%), muscle spasms (12.7%), fatigue (33.6%; Grade 3-4: 6.7%), pyrexia 23.1%; Grade 3-4: 2.2%), peripheral oedema (15.7%), and asthenia (14.2%; Grade 3-4: 3%).

The side effects observed in patients with multiple myeloma, myelodysplastic syndrome and mantle cell lymphoma are listed below by organ system and frequency. The side effects are stated in descending order of severity within each frequency group.

Frequency data: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare: (<1/10000).

Infections and infestations

Very common: Bronchitis (47.4%), nasopharyngitis (34.8%), upper respiratory tract infections (26.8%), gastroenteritis (22.5%), neutropenic infection (17.9%), pneumonia (17.1%), rhinitis (15.0%), sinusitis (14.0%), influenza (13.3%), urinary tract infections (11.6%),

Common: Bacteremia, sepsis, local and systemic infections (bacterial, viral or fungal), oral candidiasis, respiratory tract infection, lung infection, lower respiratory tract infection, enterocolitis infections .

Uncommon: Atypical pneumonia, *Pneumocystis carinii* pneumonia, subacute endocarditis, ophthalmic herpes, herpes zoster, ear infections, oesophageal candidiasis, viral reactivation* (hepatitis B virus or herpes zoster).

Very rare: Progressive multifocal leukoencephalopathy*.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Common: Acute myeloid leukemia, myelodysplastic syndrome, squamous cell carcinoma, basal cell carcinoma, tumor lysis syndrome, tumor flare reaction.
Uncommon: Acute T-cell type leukemia

Blood and lymphatic system disorders

Very common: Neutropenia (79.0%), thrombocytopenia (72.3%), anaemia (43.8%), leukopenia (31.7%), lymphopenia (17.9%), febrile neutropenia (17.4%).
Common: Pancytopenia,
Uncommon: granulocytopenia, haemolytic anaemia, prolonged coagulation, monocytopenia, leucocytosis, lymphadenophathy.

Immunesystem disorders

Uncommon: Acquired hypogammaglobulinaemia. *angioedema**, acute graft-versus-host reaction*

Not known: Organ transplant rejection*.

Endocrine Disorders

Common: Cushing syndrome.
Uncommon: Adrenal insufficiency, hypothyroidism, hyperthyroidism elevated or reduced TSH, hirsutism.

Metabolism and nutrition disorders

Very common: Hypocalcaemia (50.0%), decreased appetite (34.4%, hyponatraemia (30.5%), hypokalaemia (29.0%), dehydration (16.4%), weight loss (13.5%), hyperglycaemia (11.7%) hypoglycaemia (10.7%).
Common: Anorexia,hypomagnesaemia, fluid retention, weight gain, iron overload.
Uncommon: Metabolic acidosis, diabetes mellitus, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, gout, hypophosphataemia, hyperphosphataemia, increased appetite.

Psychiatric disorders

Very common:	Insomnia (32.8%), depression (10.9%).
Common:	Confusional state, hallucinations, mood swings, anxiety, irritability, drowsiness.
Uncommon:	Psychotic disorders, hypomania, delusions, decreased libido, personality changes, nervousness, aggression, nightmares.

Nervous system disorders

Very common:	Peripheral neuropathy (71.8%), dysgeusia (30.2%), headache (14.5%), paresthesia (22.5%), dizziness (29.4%), headache (15.4%).
Common:	Cerebral ischaemia, syncope, light-headedness, tremor, memory disorders, neuralgia, dysaesthesia.
Uncommon:	Cerebrovascular accident, leukoencephalopathy, speech disorders, attention deficit disorder, vestibular disorder, movement disorder, oral paraesthesia, psychomotor hyperactivity, anosmia, ataxia, dyskinesia, motor dysfunction, myasthenic syndrome.

Eye disorders

Very common:	Vision blurred (16.0%), cataract (13.7%).
Common:	Visual disturbances, increased lacrimation, conjunctivitis.
Uncommon:	Blindness, retinal arteriosclerosis, retinal venous thrombosis, keratitis, eye irritation, dry eye.

Ear and labyrinth disorders

Common:	Vertigo.
Uncommon:	Deafness, hearing loss, tinnitus, earache.

Cardiac disorders

Common:	Atrial fibrillation, *myocardial infarction** cardiac failure.
Uncommon:	Congestive heart failure, heart valve incompetence, atrial flutter, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, pulmonary oedema, arrhythmia.

Vascular disorders

Very common:	Hypotension (16.4%), deep vein thromboses (10.2%).
Common:	Hypertension, flushing, haematoma
Uncommon:	Circulatory collapse, ischaemia, phlebitis.

Respiratory , thoracic and mediastinal disorders

Very common:	Dyspnoea (30.5%), cough (29.4%).
Common:	Pulmonary embolism, respiratory distress, pleuritic pain, hypoxia, oropharyngeal pain, epistaxis,dysphonia, hoarseness, hiccup,rhinorrhoea.

Uncommon:	Asthma, chest pain.
Rare:	Interstitial pneumonitis.

Gastrointestinal disorders

Very common:	Constipation (56.1%), diarrhoea (54.5%), nausea (37.4%), dyspepsia (19.1%), vomiting (17.6%), abdominal pain (14.0%), stomatitis (12.2%), dry mouth (11.5%).
Common:	Small intestinal obstruction, gastritis, abdominal distension, upper abdominal pain, , flatulence.
Uncommon:	Gastrointestinal bleeding, colitis, proctitis, dysphagia, haemorrhoids, oral pain, gingival bleeding.
Rare:	*Pancreatitis**

Hepatobiliary disorders

Very common:	Abnormal liver function tests such as alanine aminotransferase increased (ALT; 25.6%), aspartate aminotransferase (AST) increased (21.4%) or hyperbilirubinaemia (15.2%); blood alkaline phosphatase increased (25.2%).
Common:	Hepatocellular injury, hepatotoxicity.
Uncommon:	Hepatic failure
Not known:	Acute hepatic failure, hepatitis toxic, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis

Skin and subcutaneous tissue disorders

Very common:	Rash (31.7%), pruritus (27.5%), dry skin (10.6%).
Common:	Facial oedema, erythema, folliculitis, hyperpigmentation, exanthema, increased perspiration, hair loss, night sweats.
Uncommon:	Erythema nodosum, urticaria, eczema, hyperkeratosis, skin fissures, acne, lichen sclerosus, photosensitivity reaction, burning skin sensation, desquamation.
Rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis
Very rare:	Drug reaction with eosinophilia and systemic symptoms*.

Musculoskeletal and connective tissue disorders

Very common:	Muscle spasms (33.4%), back pain (32.0%), muscle cramps (20.1%), arthralgia (19.0%), pain in extremity (17.9%), myalgia (14.9%), musculoskeletal pain (14.8%), bone pain (11.8%), musculoskeletal chest pain (11.3%),
Common:	Myopathy, peripheral swelling, neck pain.
Uncommon:	Osteonecrosis, muscle atrophy, spondylitis, joint swelling, skeletal muscle stiff-ness, local swelling.

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Renal and urinary disorders

Common:	Renal insufficiency, renal failure (including acute).
Uncommon:	Frequent urination, renal tubular necrosis, urinary retention, acquired Fanconi syndrome, urinary incontinence.

Reproductive system and breast disorders

Common:	Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain.

General disorders and administration site conditions

Very common:	Fatigue (73.7%), peripheral oedema (46.6%), asthenia (29.7%), pyrexia (23.1%),
Common:	Falls, chills, non cardiac chest pain, contusion.
Uncommon:	Thirst, cold sensation,

* = Post-marketing experience

To report any side effect(s):

Saudi Arabia:

- The National Pharmacovigilance and Drug Safety Centre (NPC)
Fax: +966-11-205-7662
Call NPC at +966-11-2038222, Exts: 2317-2356--2340. SFDA Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

United Arab Emirates:

Pharmacovigilance and Medical Device Section
P.O. Box: 1853 Dubai UAE
Tel: 80011111
Email: pv@moh.gov.ae
Drug Department and Prevention
Ministry of Health & Prevention
Dubai

Oman:

Department of Pharmacovigilance & Drug Information
Directorate General of Pharmaceutical Affairs & Drug Control
Ministry of Health, Sultanate of Oman
Phone Nos. 00968 22357686/00968 22357687
Fax: 00968 22358489
Email: dg-padc@moh.gov.om
Website: www.moh.gov.om

· ***Other Countries:***

- Please contact the relevant competent authority.

4.9 Overdose

In the studies, the dose-limiting toxicity was essentially haematological. In the event of overdose, monitoring (clinical, laboratory) as well as supportive measures are indicated.

Lenalidomide is only slightly dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: L04AX04.

Mechanism of action /Pharmacodynamics

Lenalidomide is a derivative of thalidomide and exists as a racemate. It possesses both immunomodulating and antiangiogenic properties.

Lenalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and Roc1, and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins and may explain the pleiotropic cellular effects observed with lenalidomide treatment.

Lenalidomide inhibits the release of proinflammatory cytokines including tumour necrosis factor α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-12 from the lipopolysaccharide (LPS)–stimulating mononuclear cells of the peripheral blood and increases the formation of the anti-inflammatory cytokine IL-10 in LPS-stimulated cells.

It induces the production of IL-2 and interferon-1γ (IFN-1γ) and increases the proliferation of T cells as well as the cytotoxic activity of the natural killer cells.

Lenalidomide inhibits the proliferation of various haematopoietic tumour cell lines.

In *in vitro* angiogenesis models lenalidomide inhibits angiogenesis by preventing the development of microvessels and endothelial cell channels as well as the migration of endothelial cells. In addition, lenalidomide inhibits the formation of proangiogenic factors VEGF in PC3 prostate tumour cells.

Cardiac Electrophysiology QT study

At single doses of 10 mg or 50 mg of lenalidomide in healthy male subjects, no prolongation of the QTc interval could be associated.

ClinicalEfficacy

Clinical experience with lenalidomide in combination with bortezomib and dexamethasone in untreated patients with multiple myeloma who are eligible for transplant

The efficacy (as per the International Myeloma Working Group (IMWG) response criteria) and safety of lenalidomide in combination with bortezomib and dexamethasone (RVd) were assessed in two multicentre, phase 3 clinical studies: PETHEMA GEM2012 and IFM 2009.

PETHEMA GEM2012

The PETHEMA GEM2012 study was a randomised, controlled, open-label, multicentre phase 3 study, in which 2 conditioning regimens (busulfan-melphalan and MEL200), administered prior to transplantation in patients who had received RVd as initial therapy, were compared with each other. RVd was given in six 4-week cycles (24 weeks). The patients received lenalidomide 25 mg/day orally on days 1-21, subcutaneous bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11, plus dexamethasone 40 mg/day orally on days 1-4 and 9-12 of the repeated 28-day cycles. Following initial treatment, the patients received either a conditioning regimen with busulfan-melphalan or with MEL200 (1:1 randomisation) and ASCT. The patients also received two additional treatment cycles (8 weeks) with RVd following ASCT. In total, 458 patients were enrolled into the study.

In the PETHEMA GEM2012 study, at the end of initial treatment with RVd, the ≥ VGPR rate was 67% and the CR rate was 33%, with 47% (217/458) of study participants MRD negative. Of those study participants with ≥ VGPR, 64% (196/305) were MRD negative (10^{-4} sensitivity).

The post-transplant ≥ VGPR rate was 75% and the CR rate was 44%, with 59% (287/458) of study participants MRD negative. Of those study participants with ≥ VGPR, 79% (271/344) were MRD negative (10^{-4} sensitivity).

IFM 2009

The IFM 2009 study was a randomised, controlled, open-label, multicentre phase 3 study to compare RVd with and without ASCT as initial therapy in patients with previously untreated multiple myeloma who were eligible for transplant. The patients received lenalidomide 25 mg/day orally on days 1-14, intravenous bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11, plus 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 as three 3-week cycles (9 weeks) before ASCT (Arm B). The patients in Arm B also received two additional 3-week cycles of RVd following ASCT. In total, 700 patients were enrolled into the study.

In the IFM 2009 study, at the end of initial therapy, the ≥ VGPR rate was 68% and the CR rate 31%. Of those study participants with ≥ VGPR, 57% (136/237) were MRD negative (10^{-4} sensitivity).

Clinical experience with lenalidomide in patients with multiple myeloma following autologous stem cell transplantation

The efficacy and safety of lenalidomide was assessed in two phase 3 multicenter, randomized, double-blind 2- arm, parallel group, placebo-controlled studies: CALGB 100104 and IFM 2005-02. The primary endpoint of both studies was PFS.

CALGB100104

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

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

In total 460 patients were randomised: 231 patients to lenalidomide and 229 patients to placebo. The demographic and disease-related characteristics were balanced across both arms.

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

The median follow-up for surviving patients at the cutoff date of 01 February 2016 was 81.9 months. There was a 39% reduction in risk of disease progression or death favoring lenalidomide (HR = 0.61; 95% CI, 0.48 to 0.76; p < 0.001). The PFS was 56.9 months in the lenalidomide group versus an estimated 29.4 months in the placebo arm.

For the OS analysis, the observed HR was 0.61 (95% CI, 0.46 to 0.81) for lenalidomide versus placebo indicating a 39% reduction in the risk of death. The median overall survival time (based on the Kaplan-Meier estimate) was 111.0 month in the lenalidomide group versus 84.2 months in the placebo arm.

IFM 2005-02
Patients were aged < 65 years at diagnosis and had undergone treatment with high-dose chemotherapy followed by ASCT and had achieved at least a stable disease response at the time of hematologic recovery.

Within 6 months after ASCT, patients were randomized to receive either lenalidomide or placebo maintenance therapy. Following 2 courses of lenalidomide consolidation (25 mg/day, Days 1-21 of a 28-day cycle), the lenalidomide maintenance dose was 10 mg once daily (Days 1-28 of a 28-day cycle; increased to 15 mg once daily after 3 months for patients who tolerated therapy). Treatment was continued until disease progression.In total 614 patients were randomised: 307 patients to Lenalidomide and 307 patients to placebo.
Treatment was stopped for the remaining 119 subjects receiving lenalidomide maintenance (minimum treatment duration of 27 months) due to an observed imbalance of SPMs.

The median follow-up for surviving subjects at the cutoff date of 01 February 2016 was 96.7 months. There was a 43% reduction in risk of disease progression or death favoring lenalidomide (HR = 0.57; 95% CI, 0.42 to 0.76; p < 0.001). The progression-free survival time was 44.4 months in the lenalidomide group versus 23.8 months in the placebo arm.

For OS, the observed HR was 0.90 (95% CI, 0.72 to 1.13) for lenalidomide versus placebo. The median overall survival time was 105.9 months in the lenalidomide arm versus 88.1 months in the placebo arm.

Clinical experience with lenalidomide in combination with dexamethasone in untreated patients who are not eligible for transplant

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

Patients in the Rd and Rd18 arms took lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles according to protocol arm. Dexamethasone 40 mg was dosed once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Initial dose and regimen for Rd and Rd18 were adjusted according to age and renal function. 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 acetylsalicylic acid) 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 randomized to Rd, 541 patients randomized to Rd18 and 547 patients randomized to MPT. The demographics and disease-related base-line 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

PFS was significantly longer with Rd (26.0 month) than MPT (21.9 month): HR 0.69 (95% CI: 0.59-0.80 p = < 0.001) indicating a 31% reduction in the risk of disease progression or death. The same proportion (10%) of on-study death events contributed to PFS in both treatment arms. The improvement in median PFS time in the Rd arm compared with the MPT arm was 4.3 months. The myeloma response rate was significantly higher with Rd compared with MPT (75.1% versus 62.3%; p < 0.00001) with a complete

response in 15.1% of patients in the Rd arm versus 9.3% of patients in the MPT arm. The median time to first response was 1.8 months in Rd arm versus 2.8 months in the MPT arm.

For the OS analysis, the median follow-up time for all surviving patients is 37.0 months, with 574 death events, at 64% occurrence (574/896) of the final OS events. The observed HR was 0.78 for Rd versus MPT (95% CI = 0.64, 0.96; nominal p = 0.01685) indicating a 22% reduction in the risk of death.

Clinical experience with lenalidomide in combination with melphalan and prednisone in untreated patients who are not eligible for transplant

The safety and efficacy of lenalidomide was assessed in a Phase III multicenter, randomized double blind 3 arm study (MM-015) of patients who were 65 years or older and had a serum creatinine < 2.5 mg/dL. The study compared lenalidomide in combination with melphalan and prednisone (MPR) with or without lenalidomide maintenance monotherapy until disease progression, to that of melphalan and prednisone for a maximum of 9 cycles. Patients were randomized in a 1:1:1 ratio to one of 3 treatment arms: Arm MPR+R – oral MPR induction combination therapy followed by lenalidomide maintenance therapy; Arm MPR+ p – oral MPR induction combination therapy followed by placebo maintenance treatment; or Arm MPp+ p – oral MPp (MP + placebo) induction combination therapy followed by placebo maintenance treatment.

PFS was according a blinded independent review significantly longer with MPR+R than MP+p with a HR 0.388 (95% CI: 0.274-0.550) indicating a 61% reduction in the risk of disease progression or death compared to MPp+p.

Clinical experience in patients with multiple myeloma who received at least one prior therapy

In two multicentre, randomised, placebo-controlled, parallel group controlled, double-blind studies of identical design (MM-009 in the USA and Canada or MM-010 in Europe, Israel and Australia) 353 and 351 patients, respectively, with multiple myeloma, previously treated with one or more chemotherapy regimens, were treated either with lenalidomide plus dexamethasone or with dexamethasone alone.

In a pooled analysis of both studies, the median time to progression (TTP) was 48 weeks (95% CI: 41.1; 60.1) in patients treated with lenalidomide/dexamethasone and 20.1 weeks (95% CI: 19.9, 20.7) in patients treated with placebo/dexamethasone. The median duration of progression-free survival was 47.3 weeks (95% CI: 36.9, 58.4) *versus* 20.1 weeks (95% CI: 18.1, 20.3). The overall survival in patients treated with lenalidomide/dexamethasone was significantly higher at 90.3 vs 80.2 weeks, p=0.015, (patients in the placebo arm could, after progression and after unblinding, change to the active arm; 50% were treated with lenalidomide/dexamethasone).

The median duration of treatment was 28.1 weeks (min: 0.1, max: 110.7).

Clinical experience in myelodysplastic syndrome

In a multicentre, single-arm, open phase II study (MDS-003 in Germany and the USA), 120 patients with confirmed erythrocyte transfusion dependence due to MDS with a low or intermediate risk 1 with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities were treated with lenalidomide 10 mg. The median duration of treatment was 52.5 weeks. The rate of transfusion-independence (> 56 days) was 62.8%. The median increase in haemoglobin was 5.9 g/dl. The median duration of response was 97 weeks. A clear cytogenetic response was observed in 34.6% of the patients and a less pronounced cytogenetic response was observed in 38.5% of the patients.

In a multicentre, double-blind, placebo-controlled, three-arm phase III study (MDS-004 in Europe and Israel), 138 patients with confirmed erythrocyte transfusion dependence due to MDS with a low or intermediate risk 1 with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities were treated with lenalidomide 10 mg, lenalidomide 5 mg or placebo, according to randomisation. The duration of the double-blind phase was 16-52 weeks. The rate of transfusion-independence (> 182 days) was 56.1% in the 10 mg group. The corresponding transfusion-independence rates in the 5 mg and placebo groups were 41.3% and 5.9%, respectively. The median duration of repsonse was 106 weeks in the 10 mg group; in the 5 mg and placebo groups, in contrast, it could not be determined. A clear and less pronounced cytogenetic response was observed in 24.0% and 17.1% of the patients, respectively, in the 10 mg group, 10.9% and 6.5%, respectively, in the 5 mg group and 0% and 0%, respectively, in the placebo group.

The rate of transfusion-independence (> 56 days) in the 10 mg group was 61.0%, with a median increase in haemoglobin of 6.3 g/dl. The corresponding transfusion-independence rates and haemoglobin increases in the 5 mg and placebo groups were 50.0% and 7.8%, respectively, and 5.1 g/dl and 2.3 g/dl, respectively.

Clinical experience in mantle cell lymphoma

MCL-001 was a Phase 2, multicenter, uncontrolled study of single-agent lenalidomide designed to evaluate the safety and efficacy of lenalidomide in patients with mantle cell lymphoma who have relapsed after or were refractory to bortezomib or a bortezomib-containing regimen. Only patients with documented translocation or cyclin-overexpression as well as patients not eligible for stem cell transplant were included in the study. Lenalidomide was given on days 1-21 of repeated 28-day cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Patients were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination.

Patients were enrolled with absolute neutrophil counts (ANC) ≥ 1500 cells/mm^3, platelet counts ≥ 60,000/cells/mm^3, serum SGOT/AST or SGPT/ALT < 3.0 x upper limit of normal (ULN) unless there was documented evidence of liver involvement by lymphoma, serum total bilirubin < 1.5 x ULN except in cases of Gilbert's syndrome or documented liver involvement by lymphoma, and calculated creatinine clearance (Cockcroft-Gault formula) >30 ml/min.

The primary efficacy endpoints in MCL-001 were overall response rate (ORR) and duration of response (DOR). An overview of the efficacy results for the Intent to Treat (ITT) population by Independent Review Committee (IRC) review is presented in the table below. The median time to response was 2.2 month (1.7; 13.1 month). The median overall survival was 19.0 month (95% CI 12.5; 22.9 month). The progression-free survival over the whole study population was 3.95 month.

Response Analyses (N = 134)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR+CRu+PR)	37 (28)	(20.2; 36.0)
Complete Response (CR+CRu)	10 (7)	(3.6; 13.3)
CR	2 (1)	
CRu	8 (6)	
Partial Response (PR)	27 (20)	
Stable Disease (SD)	39 (29)	

Duration of Response (months)	**Median**	**95% CI**
Duration of Overall Response (CR + CRu + PR) N = 37	16.6	(7.7; 26.7)

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

5.2 Pharmacokinetic properties

Absorption

Lenalidomide is rapidly absorbed with a T_{max} of 1 hour. The oral bioavailability is about 70%. The pharmacokinetics of lenalidomide are dose-proportional.

Co-administration with a high-fat 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.

Population pharmacokinetic studies showed, that the oral absorption of lenalidomide in MCL-patients is comparable to the absorption observed in patients with MM or MDS.

Distribution

The binding of lenalidomide to plasma proteins is low (<30%). It has not been investigated whether or not lenalidomide crosses the blood-brain barrier.

Lenalidomide is present in semen (< 0.01% of the dose) after administration of 25 mg/day. Lenalidomide is undetectable in the semen of healthy volunteers 3 days after discontinuation of the medicinal product.

Metabolism

Metabolism of lenalidomide is minor and not occurring via the phase I enzymes. Unchanged lenalidomide is the main circulating component *in vivo* in humans. Two identified metabolites are hydroxyl-lenalidomide and N-acetyl-lenalidomide; each constituting less than 5% of the blood levels of the parent substance.

Elimination

Approximately two thirds of a dose of lenalidomide is eliminated unchanged via the kidneys. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent. At therapeutic doses (up to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and ranged from 3 to 5 hours in patients. Steady state concentrations are reached on day 4. Accumulation does not occur with multiple doses.

Kineticsinspecialpatientgroups

There are no data available about the pharmacokinetics in paediatric patients.

Lenalidomide is eliminated primarily as an unchanged active substance via glomerular filtration and active tubular secretion. After a single dose of 25 mg in mild renal insufficiency (ClCr 80-50 ml/min), the AUC is increased by 25%; in moderate renal insufficiency (ClCr 50-30 ml/min) the AUC is increased 3-fold, and in severe renal insufficiency (ClCr <30 ml/min) and/or renal insufficiency requiring dialysis (interdialysis period) the AUC is increased 4- to-5-fold. The elimination half-life is increased in moderate renal insufficiency 3-fold to 9-10 hours.

Pharmacokinetics in patients with hepatic insufficiency

Population pharmacokinetic analysis included patient with weak hepatic insufficiency (N=16; total bilirubin >1.0 to ≤ 1.5 x ULN or AST > ULN) and showed that a week hepatic insufficiency doesn't influence the Lenalidomide disposition. No data are available for patient with moderate to heavy hepatic insufficiency.

5.3 Preclinical safety data

Lenalidomide demonstrates a low potential for acute toxicity; in rodents the lowest lethal doses after oral administration were more than 2000 mg/kg. Long-term administration of lenalidomide to rats led, most conspicuously in female animals, to mineralisation of the renal pelvis. The dose at which no side effects occurred (*no observed adverse effect level,* NOAEL), is estimated to be less than 75 mg/kg for rats and thus, based on the AUC, is about 25 times higher than the daily human exposure at a dose of 25 mg/day. In monkeys, repeated oral administration led to a dose-dependent decrease in the neutrophil count; this effect is due to the pharmacodynamic action of the active substance. Repeated oral administration of 4 and 6 mg/kg to monkeys over a period of up to 20 weeks led to mortality and significant toxicity (marked weight loss, decreased red and white blood cell counts as well as a decrease in the platelet count, multiple organ haemorrhage, inflammation of the gastrointestinal tract, atrophy of the lymphatic tissue and the bone marrow). Administration of 1 and 2 mg/kg/day to monkeys for 52 weeks led to changes in the cell count of the bone marrow, a slight decrease in the ratio of myeloid to erythroid cells and to thymus atrophy. At 1 mg/kg/day a slight suppression of the leukocyte count was observed. The NOAEL was 1 mg/kg/day. The AUC exposure at this dose corresponds to human therapeutic exposure at 25 mg/day.

Mutagenicity studies *in vitro* (bacterial mutations, human lymphocytes, mouse lymphoma, Syrian hamster embryo cell transformation) and *in vivo* (micronucleus test in rats) showed no effects of the active substance either at the genetic level or at the chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity (embryofetal toxicity/teratogenicity) studies were conducted in rats, rabbits and monkeys. In a study in monkeys, lenalidomide was administered in doses of up to 4 mg/kg/day. The results show that the administration of lenalidomide to pregnant monkeys led to malformations in the offspring which were similar to the malformations produced by thalidomide.

In rabbits that received oral doses of 3, 10 and 20 mg/kg/day, developmental toxicity at 10 and 20 mg/kg/day was characterized by slightly reduced fetal body weight, an increased incidence of post implantation loss (early and late resorption and intrauterine death) and macroscopic external findings in the fetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body). At 10 and 20 mg/kg/day, fetuses were observed to have soft tissue and skeletal changes but which are typical of the strain of rabbit used. In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day.

As is known from previous thalidomide studies in rats, an embryo-fetal development study in rats with lenalidomide doses up to 500 mg/kg/day also revealed no teratogenic effects. At 100, 300 or 500 mg/kg/day there was minimal maternal toxicity that included a slight, transient reduction in mean body weight gain and food intake.

6. Pharmaceutical particulars

6.1 List of excipients

Capsulecontents
Anhydrous lactose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store below 30°C. Store in the original package and out of the reach and sight of children.

6.5 Nature and contents of container

Lenalidomide capsules are provided in Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) blisters with push-through aluminium foil.

Revlimid 5 mg/ 10 mg/ 15 mg/ 25 mg hard capsules
Pack size of 21 capsules.

6.6 Special precautions for disposal and handling

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

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

7. Marketing authorisation holder

Celgene International Sàrl,

Route de Perreux 1,

2017 Boudry,

Switzerland

8. Marketing authorisation number(s)

9. Date of first Authorisation

10. Date of last revision of the text

May 2019

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