Package Insert

1. NAME OF THE MEDICINAL PRODUCT

Lenli 5 mg capsules
Lenli 10 mg capsules
Lenli 15 mg capsules
Lenli 25 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lenli 5 mg capsules
Each capsule contains 5 mg of lenalidomide.
Excipient with known effect:
Each capsule contains 107 mg of lactose.

Lenli 10 mg capsules
Each capsule contains 10 mg of lenalidomide.
Excipient with known effect:
Each capsule contains 214 mg of lactose and 0.0436 mg tartrazine (E102).

Lenli 15 mg capsules
Each capsule contains 15 mg of lenalidomide.
Excipient with known effect:
Each capsule contains 120 mg of lactose and 0.0032 mg tartrazine (E102).

Lenli 25 mg capsules
Each capsule contains 25 mg of lenalidomide.
Excipient with known effect:
Each capsule contains 200 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lenli 5 mg capsules
A green opaque cap/light brown opaque body, capsule shell size No. 2, 17.50-18.50 mm, imprinted in black ink with “LP” on the cap and “638” on the body and filled with white powder.

Lenli 10 mg capsules
A yellow opaque cap/grey opaque body, capsule shell size No. 0, 21.20-22.20 mm, imprinted in black ink with “LP” on the cap and “639” on the body and filled with white powder.

Lenli 15 mg capsules
A brown opaque cap/grey opaque body, capsule shell size No. 2, 17.50-18.50 mm, imprinted in black ink with “LP” on the cap and “640” on the body and filled with white powder.

Lenli 25 mg capsules
A white opaque cap/white opaque body, capsule shell size No. 0, 21.20-22.20 mm, imprinted in black ink with “LP” on the cap and “642” on the body and filled with white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Lenalidomide as combination therapy with dexamethasone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

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

4.2 Posology and method of administration

Lenalidomide treatment should only be prescribed by Specialist Physician experienced in the management of malignancies, who have undergone the Lenli educational programme on Pregnancy Prevention Programme.

Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma (MM).

For the indication described below:
- Dose is modified based upon clinical and laboratory findings (see section 4.4).
- Dose adjustments, during treatment and restart of treatment, are recommended to manage grade 3 or 4 thrombocytopenia, neutropenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
- In case of neutropenia, the use of growth factors in patient management should be considered.
- If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Posology
Newly diagnosed multiple myeloma (NDMM)
- Lenalidomide maintenance in patients who have undergone autologous stem cell transplantation (ASCT)

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the Absolute Neutrophil Count (ANC) is $<1.0 \times 10^9$/L, and/or platelet counts are $<75 \times 10^9$/L.

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

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

When platelets	Recommended course
Fall to $<30 \times 10^9$/L	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9$/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below 30×10^9/L	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9$/L	Resume lenalidomide at next lower dose level once daily

- *Absolute neutrophil count (ANC) - neutropenia*

When ANC	Recommended course[a]
Fall to $<0.5 \times 10^9$/L	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9$/L	Resume lenalidomide at dose level -1 once daily
For each subsequent drop below $<0.5 \times 10^9$/L	Interrupt lenalidomide treatment
Return to $\geq 0.5 \times 10^9$/L	Resume lenalidomide at next lower dose level once daily.

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

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

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

Recommended dose

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

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

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

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

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

- *Absolute neutrophil count (ANC) - neutropenia*

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

For hematologic toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no hematologic toxicity for at least 2 consecutive cycles: ANC $\geq 1.5 \times 10^9$/L with a platelet count $\geq 100 \times 10^9$/L at the beginning of a new cycle).

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

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

- *Dose reduction steps*

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

- *Thrombocytopenia*

When platelets	Recommended course
First fall to <30 x 10^9/L Return to ≥30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at dose level -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. Do not dose below 5 mg once daily.

- *Absolute neutrophil count (ANC) - neutropenia*

When ANC	Recommended course
First fall to < 1.0 x 10^9/L Return to ≥ 1.0 x 10^9/L when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at starting dose once daily
Return to ≥ 1.0 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 < 1.0 x 10^9/L Return to ≥ 1.0 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (dose level -1, -2 or -3) once daily. Do not dose below 5 mg once daily.

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

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

Special populations
- Paediatric population

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

• Elderly

Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age (see section 5.1).

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

Newly diagnosed multiple myeloma: patients who are not eligible for transplant

Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

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

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

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

Multiple myeloma: patients with at least one prior therapy

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

• Patients with renal impairment

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

No dose adjustments are required for patients with mild renal impairment.

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

There are no phase III trial experiences with End Stage Renal Disease (ESRD) (CLcr <30 mL/min, requiring dialysis).

Multiple myeloma

Renal function (CLcr)	**Dose adjustment** (days 1 to 21 of repeated 28-day cycles)
Moderate renal impairment (30≤ CLcr <50 mL/min)	10 mg once daily[1]
Severe renal impairment (CLcr <30 mL/min, not requiring dialysis)	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.

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

• Patients with hepatic impairment

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

Method of administration

Oral use.

Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

When lenalidomide is given in combination with other medicinal products, the corresponding Package Insert must be consulted prior to initiation of treatment.

Pregnancy warning

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

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

Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥50 years and naturally amenorrhoeic for ≥1 year (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy

- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

For male patients taking lenalidomide, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the substance in the healthy subject (see section 5.2). As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for at least 4 weeks after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking Lenalidomide or shortly after he has stopped taking Lenalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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

Contraception

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

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

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamtheasone, and to a lesser extent in patients with multiple myeloma taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

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

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

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

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

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

Patients should not donate blood during therapy or for at least 4 weeks following discontinuation of lenalidomide.

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the marketing authorisation holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate Patient Medication Guide. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks, and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks.

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

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism).

In patients with multiple myeloma, treatment with lenalidomide monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) than in patients with multiple myeloma treated with lenalidomide in combination therapy (see sections 4.5 and 4.8).

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). The risk of arterial thromboembolism is lower in patients with multiple myeloma treated with lenalidomide monotherapy than in patients with multiple myeloma treated with lenalidomide in combination therapy.

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

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

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

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose interruption and/or a dose reduction may be required (see section 4.2).

In case of neutropenia, the physician should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes.
Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving concomitant medicinal products susceptible to induce bleeding (see section 4.8, Haemorrhagic disorders).
Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

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

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

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

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

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

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

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

- Multiple myeloma: patients with at least one prior therapy

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

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

Thyroid disorders

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

Peripheral neuropathy

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

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

Tumour flare reaction and tumour lysis syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and uncommonly in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to lenalidomide. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide.

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Severe cutaneous reactions including SJS, and TEN and DRESS have been reported with the use of lenalidomide. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.
Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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

In clinical trials of newly diagnosed multiple myeloma patients not eligible for transplant, a 4.9-fold increase in incidence rate of hematologic SPM (cases of AML, MDS) has been observed in patients receiving lenalidomide in combination with melphalan and prednisone until progression (1.75 per 100 person-years) compared with melphalan in combination with prednisone (0.36 per 100 person-years).

A 2.12-fold increase in incidence rate of solid tumour SPM has been observed in patients receiving lenalidomide (9 cycles) in combination with melphalan and prednisone (1.57 per 100 person-years) compared with melphalan in combination with prednisone (0.74 per 100 person-years).

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate (0.16 per 100 person-years) was not increased as compared to thalidomide in combination with melphalan and prednisone (0.79 per 100 person-years).

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

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

The incidence rate of hematologic malignancies, most notably AML, MDS and B-cell malignancies (including Hodgkin's lymphoma) was 1.31 per 100 person-years for the lenalidomide arms and 0.58

per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour SPMs was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).

The risk of occurrence of hematologic SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

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

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

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

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

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

Some of the cases of viral reactivation had a fatal outcome.

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

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

Progressive multifocal leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.
The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.
If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

Solid Organ Transplant Rejection
Cases of solid organ transplant (SOT) rejection have been reported in the post-market setting with the use of lenalidomide and, in some cases, have resulted in a fatal outcome. Onset may be acute, occurring within 1 to 3 cycles of lenalidomide treatment. Potential contributing factors for SOT rejection in the reported cases include underlying disease (e.g., amyloidosis), concurrent infections and recent discontinuation or reduction of immunosuppressive therapy. The incidence rate of SOT rejection cannot be reliably estimated due to the limitation of post-marketing safety data and that patients with SOT were generally excluded from lenalidomide clinical trials. The benefit of treatment with lenalidomide versus the risk of possible SOT rejection should be considered in patients with a history of SOT before initiating lenalidomide therapy.
Clinical and laboratory signs of SOT rejection should be closely monitored and lenalidomide therapy should be discontinued in the event of SOT rejection.

- Newly diagnosed multiple myeloma patients

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

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

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

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

[*For 10 mg and 15 mg strength*]
Lenalidomide capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

4.5 Interaction with other medicinal products and other forms of interaction

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

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

Women of childbearing potential/ Contraception in males and females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a

partner of a male patient taking lenalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

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

Pregnancy
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.
Lenalidomide induced in monkeys malformations similar to those described with thalidomide (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, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Newly diagnosed multiple myeloma patients who have undergone ASCT treated with lenalidomide maintenance
A conservative approach was applied to determine the adverse reactions from CALGB 100104. The adverse reactions described in Table 1 included events reported post-HDM/ASCT as well as events from the maintenance treatment period. A second analysis that identified events that occurred after the start of maintenance treatment suggests that the frequencies described in Table 1 may be higher than actually observed during the maintenance treatment period. In IFM 2005-02, the adverse reactions were from the maintenance treatment period only.

The serious adverse reactions observed more frequently (≥5%) with lenalidomide maintenance than placebo were:
- Pneumonias (10.6%; combined term) from IFM 2005-02
- Lung infection (9.4% [9.4% after the start of maintenance treatment]) from CALGB 100104

In the IFM 2005-02 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (60.8%), bronchitis (47.4%), diarrhoea (38.9%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), asthenia (29.7%), cough (27.3%), thrombocytopenia (23.5%), gastroenteritis (22.5%) and pyrexia (20.5%).

In the CALGB 100104 study, the adverse reactions observed more frequently with lenalidomide maintenance than placebo were neutropenia (79.0% [71.9% after the start of maintenance treatment]), thrombocytopenia (72.3% [61.6%]), diarrhoea (54.5% [46.4%]), rash (31.7% [25.0%]), upper

respiratory tract infection (26.8% [26.8%]), fatigue (22.8% [17.9%]), leucopenia (22.8% [18.8%]) and anaemia (21.0% [13.8%]).

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

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

Multiple myeloma: patients with at least one prior therapy
In two phase III placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination.

The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

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

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

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

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

System Organ Class/ Preferred Term	All ADRs/ Frequency	Grade 3−4 ADRs/ Frequency

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

System Organ Class/ Preferred Term	All ADRs/ Frequency	Grade 3−4 ADRs/ Frequency
Disorders	<u>Common</u> Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	<u>Very Common</u> Fatigue, Asthenia, Pyrexia	<u>Common</u> Fatigue, Asthenia

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

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

Table 2.
Overall reported adverse drug reactions reported in pivotal clinical studies MM-020, MM-009 and MM-010 and post-marketing data in patients with multiple myeloma treated with Lenalidomide/Dexamethasone

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	<u>Very Common</u> Pneumonia◊, Upper respiratory tract infection◊, Bacterial, viral and fungal infections (including opportunistic infections)◊, Nasopharyngitis, Pharyngitis, Bronchitis◊ <u>Common</u> Sepsis◊, Sinusitis◊ <u>Not Known†</u> Viral infections, including herpes zoster and hepatitis B virus reactivation†	<u>Common</u> Pneumonia◊, Bacterial, viral and fungal infections (including opportunistic infections)◊, Cellulitis◊, Sepsis◊, Bronchitis◊ <u>Not Known†</u> Viral infections, including herpes zoster and hepatitis B virus reactivation†
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	<u>Uncommon</u> Basal cell carcinoma^,◊, Squamous skin cancer^,◊,*	<u>Common</u> Acute myeloid leukaemia◊, Myelodysplastic syndrome◊,

		Squamous cell carcinoma of skin^,◊,** Uncommon T-cell type acute leukaemia◊, Basal cell carcinoma^,◊, Tumour lysis syndrome Rare† Tumour lysis syndrome†
Blood and Lymphatic System Disorders	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Anemia◊, Haemorrhagic disorder^, Leucopenias Common Febrile neutropenia^,◊, Pancytopenia◊ Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia Not Known† Acquired haemophilia†	Very Common Thrombocytopenia^,◊, Neutropenia^,◊, Anemia◊, Leucopenias Common Febrile neutropenia^,◊, Pancytopenia◊, Haemolytic anemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity^ Not Known† Solid organ transplant rejection†	
Endocrine Disorders	Common Hypothyroidism, Hyperthyroidism†	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia◊, Hyperglycaemia, Hypocalcaemia◊, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration◊, Hypercalcaemia‡	Common Hypokalaemia◊, Hyperglycaemia, Hypocalcaemia◊, Diabetes mellitus◊, Hypophosphataemia, Hyponatraemia◊, Hyperuricaemia, Gout, Decreased appetite, Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon	Common Depression, Insomnia

	Loss of libido	
Nervous System Disorders	Very Common Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache Common Ataxia, Balance impaired	Common Cerebrovascular accident◊, Dizziness, Syncope Uncommon Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	Very Common Cataracts, Blurred vision Common Reduced visual acuity	Common Cataract Uncommon Blindness
Ear and Labyrinth Disorders	Common Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	Common Atrial fibrillation◊, Bradycardia Uncommon Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	Common Myocardial infarction (including acute) ^,◊, Atrial fibrillation◊, Congestive cardiac failure◊, Tachycardia, Cardiac failure◊, Myocardial ischaemia◊
Vascular Disorders	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊ Common Hypotension◊, Hypertension, Ecchymosis^	Very Common Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism^,◊ Common Vasculitis Uncommon Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	Very Common Dyspnoea ◊, Epistaxis^ Uncommon Pulmonary hypertension	Common Respiratory distress◊, Dyspnoea◊ Rare Pulmonary hypertension Not Known† Interstitial pneumonitis†
Gastrointestinal Disorders	Very Common Constipation◊, Diarrhoea◊, Nausea, Vomiting, Abdominal pain◊, Dyspepsia	Common Constipation◊, Diarrhoea◊, Abdominal pain◊, Nausea, Vomiting Not Known†

	Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Dry mouth, Stomatitis, Dysphagia Uncommon Colitis, Caecitis	Pancreatitis†, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)^ †
Hepatobiliary Disorders	Common Abnormal liver function tests ◊ Uncommon Hepatic failure^ Not Known† Acute hepatic failure^,†, Hepatitis toxic^,†, Cytolytic hepatitis^,†, Cholestatic hepatitis^,†, Mixed cytolytic/cholestatic hepatitis^,†	Common Cholestasis◊, Abnormal liver function tests◊ Uncommon Hepatic failure^ Not Known† Acute hepatic failure^,†, Hepatitis toxic^,†
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes Uncommon† Angioedema† Rare† Stevens-Johnson Syndrome^†, Toxic epidermal necrolysis^† Not Known† Leukocytoclastic vasculitis†, Drug Reaction with Eosinophilia and Systemic Symptoms^†
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊), Arthralgia◊ Common Joint swelling, Muscular weakness, Myalgia	Common Muscular weakness, Bone pain◊, Musculoskeletal and connective tissue pain and discomfort (including back pain◊) Uncommon Joint swelling
Renal and Urinary	Very Common	Uncommon

Disorders	Renal failure (including acute) ◊ <u>Common</u> Haematuria^, Urinary retention, Urinary incontinence <u>Uncommon</u> Acquired Fanconi syndrome	Renal tubular necrosis
Reproductive System and Breast Disorders	<u>Common</u> Erectile dysfunction	
General Disorders and Administration Site Conditions	<u>Very Common</u> Fatigue◊, Oedema (including peripheral oedema), Pyrexia◊, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors), Asthenia <u>Common</u> Chest pain, Lethargy	<u>Common</u> Fatigue◊, Pyrexia◊, Asthenia
Investigations	<u>Common</u> C-reactive protein increased	
Injury, Poisoning and Procedural Complications	<u>Common</u> Fall, Contusion^	

^see section 4.8 description of selected adverse reactions
†reports from post-marketing data
◊Adverse reactions reported as serious in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone, or with melphalan and prednisone
‡ Applies to serious adverse drug reactions only
*Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
**Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed multiple myeloma patients with lenalidomide/dexamethasone compared to controls

<u>Description of selected adverse reactions</u>

<u>*Teratogenicity*</u>

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

<u>*Neutropenia and thrombocytopenia*</u>

- <u>Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance</u>

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

placebo maintenance arms in both studies (0.4% vs 0.5% [0.4% vs 0.5% after the start of maintenance treatment] in CALGB 100104 and 0.3% vs 0% in IFM 2005-02, respectively).

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

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

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

The combination of lenalidomide with low dose dexamethasone in newly diagnosed multiple myeloma patients is associated with a lower frequency of grade 3 and 4 thrombocytopenia (8.1% in Rd and Rd18) compared with MPT (11%).

- Multiple myeloma: patients with at least one prior therapy

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

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

Venous thromboembolism

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

Myocardial infarction

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

Haemorrhagic disorders

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

Allergic reactions

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions

Severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. Patients with a history of severe rash associated with thalidomide treatment should

not receive lenalidomide (see section 4.4).

Second primary malignancies

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

Acute myeloid leukaemia

- Multiple myeloma

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

Hepatic disorders

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

Rhabdomyolysis

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

Thyroid disorders

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

Gastrointestinal disorders

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

Acute Graft Versus Host Disease

In the literature and post-marketing setting, acute graft-versus-host disease has been reported with lenalidomide therapy following allogeneic hematopoietic transplant.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

Mechanism of action

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

Clinical efficacy and safety

Lenalidomide efficacy and safety have been evaluated in five phase III studies in newly diagnosed multiple myeloma and two phase III studies in relapsed refractory multiple myeloma as described below.

Newly diagnosed multiple myeloma

- Lenalidomide maintenance in patients who have undergone ASCT

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

CALGB 100104

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

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

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

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

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

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

The results for the study, using a cut-off of 1 February 2016, are presented in Table 3.

Table 3: Summary of overall efficacy data

	Lenalidomide (N=231)	Placebo (N=229)
Investigator-assessed PFS		
Median[a] PFS time, months (95% CI)[b]	**56.9** (41.9, 71.7)	**29,4** (20.7, 35.5)
HR [95% CI][c]; p-value[d]	**0.61** (0.48, 0.76); <0.001	
PFS2[e]		
Median[a] PFS2 time, months (95% CI)[b]	**80.2** (63.3, 101.8)	**52.8** (41.3, 64.0)
HR [95% CI][c]; p-value[d]	**0.61** (0.48, 0.78); <0.001	
Overall survival		
Median[a] OS time, months (95% CI)[b]	**111.0** (101.8, NE)	**84.2** (71.0, 102.7)
8-year survival rate, % (SE)	60.9 (3.78)	44.6 (3.98)
HR [95% CI][c]; p-value[d]	0.61 (0.46, 0.81); <0.001	
Follow-up		
Median[f] (min, max), months: all surviving patients	**81.9** (0.0, 119.8)	**81.0** (4.1, 119.5)

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

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

[b] The 95% CI about the median.

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

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

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

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

Data cuts: 17 Dec 2009 and 01 Feb 2016

IFM 2005-02

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

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

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

The results of PFS at unblinding, following a preplanned interim analysis, using a cut-off of 7 July 2010 (31.4 months follow up) showed a 48% reduction in risk of disease progression or death favouring lenalidomide (HR=0.52; 95% CI 0.41, 0.66; p <0.001). The median overall PFS was 40.1 months (95% CI 35.7, 42.4) in the lenalidomide arm versus 22.8 months (95% CI 20.7, 27.4) in the placebo arm.

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

The updated PFS, using a cut-off of 1 February 2016 (96.7 months follow up) continues to show a PFS advantage: HR=0.57 (95% CI 0.47, 0.68; p <0.001). The median overall PFS was 44.4 months (39.6,

52.0) in the lenalidomide arm versus 23.8 months (95% CI 21.2, 27.3) in the placebo arm. For PFS2, the observed HR was 0.80 (95% CI 0.66, 0.98; p=0.026) for lenalidomide versus placebo. The median overall PFS2 was 69.9 months (95% CI 58.1, 80.0) in the lenalidomide arm versus 58.4 months (95% CI 51.1, 65.0) in the placebo arm. For OS, the observed HR was 0.90: (95% CI 0.72, 1.13; p=0.355) for lenalidomide versus placebo. The median overall survival time was 105.9 months (95% CI 88.8, NE) in the lenalidomide arm versus 88.1 months (95% CI 80.7, 108.4) in the placebo arm.

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

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 older or, if younger than 65 years of age, were not candidates for stem cell transplantation because they declined to undergo stem cell transplantation or stem cell transplantation is not available to the patient due to cost or other reason. The study (MM-020) compared 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 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 randomization 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 (see section 4.2). Patients >75 years received a dexamethasone dose of 20 mg once daily on days 1, 8, 15, and 22 of each 28-day cycle. All patients received prophylactic anticoagulation (low molecular weight heparin, warfarin, heparin, low-dose aspirin) during the study.

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

In an updated analysis of PFS, PFS2 and OS using a cut off of 3 March 2014 where the median follow up time for all surviving subjects was 45.5 months, the results of the study are presented in Table 4:

Table 4: Summary of overall efficacy data

	Rd (N=535)	**Rd18 (N=541)**	**MPT (N=547)**
Investigator-assessed PFS - (months)			
Median[a] PFS time, months (95% CI)[b]	26.0 (20.7, 29.7)	21.0 (19.7, 22.4)	21.9 (19.8, 23.9)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.69 (0.59, 0.80); <0.001		
Rd vs Rd18	0.71 (0.61, 0.83); <0.001		
Rd18 vs MPT	0.99 (0.86, 1.14); 0.866		
PFS2[e] - (months)			
Median[a] PFS2 time, months (95% CI)[b]	42.9 (38.1, 47.4)	40.0 (36.2, 44.2)	35.0 (30.4, 37.8)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.74 (0.63, 0.86); <0.001		
Rd vs Rd18	0.92 (0.78, 1.08); 0.316		
Rd18 vs MPT	0.80 (0.69, 0.93); 0.004		
Overall survival (months)			

	Rd (N=535)	Rd18 (N=541)	MPT (N=547)
Median[a] OS time, months (95% CI)[b]	58.9 (56.0, NE)	56.7 (50.1, NE)	48.5 (44.2, 52.0)
HR [95% CI][c]; p-value[d]			
Rd vs MPT	0.75 (0.62, 0.90); 0.002		
Rd vs Rd18	0.91 (0.75, 1.09); 0.305		
Rd18 vs MPT	0.83 (0.69, 0.99); 0.034		
Follow-up (months)			
Median[f] (min, max): all patients	40.8 (0.0, 65.9)	40.1 (0.4, 65.7)	38.7 (0.0, 64.2)
Myeloma response[g] n (%)			
CR	81 (15.1)	77 (14.2)	51 (9.3)
VGPR	152 (28.4)	154 (28.5)	103 (18.8)
PR	169 (31.6)	166 (30.7)	187 (34.2)
Overall response: CR, VGPR, or PR	402 (75.1)	397 (73.4)	341 (62.3)
Duration of response - (months)[h]			
Median[a] (95% CI)[b]	35.0 (27.9, 43.4)	22.1 (20.3, 24.0)	22.3 (20.2, 24.9)

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

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

[b] The 95% CI about the median.

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

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

[e] Exploratory endpoint (PFS2)

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

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

[h] data cut 24 May 2013

Supportive newly diagnosed multiple myeloma studies

An open-label, randomized, multicenter, phase III study (ECOG E4A03) was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm.

Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus dexamethasone 40 mg/day on days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

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

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

Multiple myeloma with at least one prior therapy

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

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

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

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

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

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 5 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

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

Table 5: Summary of results of efficacy analyses as of cut-off date for extended follow-up — pooled studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	len/dex	placebo/dex	

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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

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

In vitro studies indicate that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion

transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

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

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the active substance during pregnancy.

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell
Lenli 5 mg capsules
Brilliant Blue FCF (E133)
Sunset Yellow FCF (E110)
Black iron oxide
Red iron oxide
Yellow iron oxide
Titanium dioxide
Gelatin

Lenli 10 mg capsules
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Tartrazine (E102)

Sunset Yellow FCF (E110)
Titanium dioxide
Gelatin

Lenli 15 mg capsules
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Tartrazine (E102)
Black iron oxide
Red iron oxide
Yellow iron oxide
Titanium dioxide
Gelatin

Lenli 25 mg capsules
Titanium dioxide
Gelatin

Printing ink
Shellac (E904)
Propylene glycol (E1520)
Strong ammonia solution (E527)
Black iron oxide (E172)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer carton.

6.4 Special precautions for storage

Please refer to outer carton.

6.5 Nature and contents of container

Carton box containing PVC/ACLAR/Al blisters of 7 capsules each.

Lenalidomide 5 mg capsules
Pack size of 7 or 21 capsules. Not all pack sizes may be marketed.

Lenalidomide 10 mg/ 15 mg/ 25 mg capsules
Pack size of 21 capsules.

6.6 Special precautions for disposal and other handling

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

LOTUS INTERNATIONAL PTE. LTD.
80 Robinson Road
#02-00
Singapore 068898

8. DATE OF REVISION OF THE TEXT

09/2022