ART025140P
LENALIDOMIDE MALAYSIA 5MG 10MG 15MG 25MG PIL

lotus PHARMACEUTICAL

GERNERAL INFORMATION

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Main contact:
Teddy Hu, Artwork Manager
teddy.hu@lotuspharm.com

REGULATORY APPROVAL

LENMICARE CAPSULES
5mg, 10mg, 15mg, 25mg

Immunosuppressant

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1. NAME OF THE MEDICINAL PRODUCT

Lenmicare Capsules 5 mg
Lenmicare Capsules 10 mg
Lenmicare Capsules 15 mg
Lenmicare Capsules 25 mg

2. QUALITATIVE AND QUANTITVATIVE COMPOSITION

Each hard capsule contains 5 mg of lenalidomide, the lactose content is 107 mg
Each hard capsule contains 10 mg of lenalidomide, the lactose content is 214 mg
Each hard capsule contains 15 mg of lenalidomide, the lactose content is 120 mg
Each hard capsule contains 25 mg of lenalidomide, the lactose content is 200 mg
For excipients, see *List of Excipients*

3. PHARMACEUTICAL FORM

Hard Capsules

Lenmicare Capsules 5 mg
A green opaque cap/light brown opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "638" on the body and filled with white powder

Lenmicare Capsules 10 mg
A yellow opaque cap/gray opaque body, capsule shell size No. 0 imprinted in black ink with "LP" on the cap and "639" on the body and filled with white powder

Lenmicare Capsules 15 mg
A brown opaque cap/gray opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "640" on the body and filled with white powder

Lenmicare Capsules 25 mg
A white opaque cap/white opaque body, capsule shell size No. 0 imprinted in black ink with "LP" on the cap and "642" on the body and filled with white powder

4. CLINICAL PARTICULARS

4.1 Indications

Lenmicare as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
Lenmicare in combination with dexamethasone is indicated for the treatment of previously untreated multiple myeloma patients who are not eligible for transplant.
Lenmicare in combination with dexamethasone is indicated for the treatment of multiple myeloma in patients who have received at least one prior therapy.

4.2 Posology and Administration

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

For all indications described below:

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

Posology

Newly diagnosed multiple myeloma (NDMM)

- Lenalidomide 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 x 10^9/L, and/or platelet counts are <75 x 10^9/L.

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

- *Dose reduction steps*

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

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

- *Thrombocytopenia*

When platelets	Recommended course
Fall to <30 x 10^9/L Return to ≥30 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at Dose level-1 once daily
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 once daily

- *Neutropenia*

When neutrophils	Recommended course[a]
Fall to <0.5 x 10^9/L Return to ≥0.5 x 10^9/L	Interrupt lenalidomide treatment Resume lenalidomide at Dose level-1 once daily
For each subsequent drop below <0.5 x 10^9/L Return to ≥0.5 x 10^9/L	Interrupt lenalidomide treatment 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 x 10^9/L, and/or platelet counts are <50 x 10^9/L.

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

- *Dose reduction steps*

	Lenalidomide	Dexamethasone
Starting dose	25 mg	40 mg
Dose level-1	20 mg	20 mg
Dose level-2	15 mg	12 mg
Dose level-3	10 mg	8 mg
Dose level-4	5 mg	4 mg
Dose level-5	5 mg every other day	NA

- *Thrombocytopenia*

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

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

- *Neutropenia*

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

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

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

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

- *Dose reduction steps*

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

- *Thrombocytopenia*

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

- *Neutropenia*

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

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

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

Special populations

- *Paediatric population*
  Lenmicare should not be used in children and adolescents from birth to less than 18 years because of safety concerns (see section 4.4).

- *Older people*
  Currently available pharmacokinetic data are described in section 5.2. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 91 years of age.
  In 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 (see section 4.4). Patients with newly diagnosed multiple myeloma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4). 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*
  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.
  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 substantially 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.

Administration
Oral use.
Lenmicare capsules should be taken 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.
- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

4.4 Warnings and Precautions

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. 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 sterilization
- 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. 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), throughout treatment duration, during dose interruption and for at least 7 days after dose interruptions and/or cessation of treatment
- Understand that if his female partner becomes pregnant whilst he is taking lenalidomide or 7 days 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 specialized or experienced in teratology for evaluation and advice

The prescriber must ensure that for women of childbearing potential:

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

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

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilization
- Sexual intercourse with a vasectomized 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 dexamethasone, and to a lesser extent in patient with multiple myeloma taking lenalidomide monotherapy, combined oral contraceptive pills are not recommended. 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.

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 has 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 sterilization. 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.

Men
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of lenalidomide.

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 (including during dose interruption) or for at least 7 days following discontinuation of lenalidomide.

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

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to lenalidomide, the marketing authorization 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 patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens, and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks.

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

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

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.

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 ATE 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 stabilized on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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

Neutropenia and thrombocytopenia
The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required. 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. 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 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. The adverse reactions were from the maintenance treatment period only.

Overall, Grade 4 neutropenia was observed at a higher frequency in the lenalidomide maintenance compared to the placebo maintenance in NDMM patients who have undergone ASCT. Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported. Patients should be advised to promptly report febrile episodes, a treatment interruption and/or dose reductions may be required.

Grade 3 or 4 thrombocytopenia was observed at a higher frequency in the lenalidomide maintenance compared to the placebo maintenance in NDMM patients who have undergone ASCT. 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.

- Newly diagnosed multiple myeloma: patients treated 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 compared. Grade 4 febrile neutropenia episodes were consistent with the comparator arm.

- 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. Grade 4 febrile neutropenia episodes were observed infrequently.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of Grade 3 and Grade 4 thrombocytopenia.

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 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. Cases of TLS and tumour flare reaction (TFR), including fatal cases, have been reported. 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.

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

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

Second primary malignancies
An increase of second primary malignancies (SPM) has been observed in previously treated myeloma patients receiving lenalidomide/dexamethasone. Non-invasive SPM comprises basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In patients receiving lenalidomide in combination with dexamethasone until progression or for 18 months, the hematologic SPM incidence rate was not increased as compared to thalidomide in combination with melphalan and prednisone.

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 compared to thalidomide in combination with melphalan and prednisone.

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 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 should initiate 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 (e.g. cough, fever, etc) thereby allowing for early management to reduce severity.

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

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

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

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

Progressive multifocal leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued.

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

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.

Sodium content
Lenmicare contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially "sodium-free".

4.5 Interactions

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 doses of 10 mg 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 Pregnancy, Lactation and Fertility

Due to the teratogenic potential, lenalidomide must be prescribed under a Pregnancy Prevention Programme 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 at least one 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 specialized 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 specialized 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. 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 at least 7 days after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

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

Lenalidomide induced malformation in monkeys similar to those described with thalidomide. Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy.

Lactation
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 and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

4.8 Side Effects

Summary of the safety profile
Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with lenalidomide maintenance
The serious adverse reactions observed more frequently (≥5%) with lenalidomide maintenance than placebo were: pneumonias and lung infection.

The adverse reactions observed more frequently with lenalidomide maintenance than placebo were: neutropenia, bronchitis, diarrhoea, nasopharyngitis, muscle spasms, leucopenia, asthenia, cough, thrombocytopenia, gastroenteritis, pyrexia, rash, upper respiratory tract infection, fatigue and anaemia.

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 than with melphalan, prednisone and thalidomide (MPT) were: pneumonia and renal failure (including acute).

The adverse reactions observed more frequently with lenalidomide in combination with low dose dexamethasone than MPT were: diarrhoea, fatigue, back pain, asthenia, insomnia, rash, decreased appetite, cough, pyrexia and muscle spasms.

Multiple myeloma: patients with at least one prior therapy
The most serious adverse reactions observed more frequently in lenalidomide/dexamethasone than placebo/dexamethasone combination were: venous thromboembolism (deep vein thrombosis, pulmonary embolism) and Grade 4 neutropenia (see section 4.4).

The observed adverse reactions which occurred more frequently with lenalidomide and dexamethasone than placebo and dexamethasone were: fatigue, neutropenia, constipation, diarrhoea, muscle cramp, anaemia, thrombocytopenia and rash.

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).

Tabulated summary for monotherapy in MM
Table 1: ADRs reported in clinical trials in patients with multiple myeloma treated with lenalidomide maintenance therapy

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonias[◊,a], Upper respiratory tract infection, Neutropenic infection, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Sinusitis, Nasopharyngitis, Rhinitis Common Infection[◊], Urinary tract infection[◊,*], Lower respiratory tract infection, Lung infection	Very Common Pneumonias[◊,a], Neutropenic Infection Common Sepsis[◊,b], Bacteraemia, Lung infection[◊], Lower respiratory tract infection bacterial, Bronchitis[◊], Influenza[◊], Gastroenteritis[◊], Herpes zoster[◊], Infection[◊]
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Common Myelodysplastic syndrome[◊,*]	
Blood and Lymphatic System Disorders	Very Common Neutropenia[◊,^], Febrile neutropenia[◊,^], Thrombocytopenia[◊,^], Anemia, Leucopenia[◊], Lymphopenia	Very Common Neutropenia[◊,^], Febrile neutropenia[◊,^], Thrombocytopenia[◊,^], Anemia, Leucopenia[◊], Lymphopenia Common Pancytopenia[◊]
Metabolism and Nutrition Disorders	Very Common Hypokalaemia	Common Hypokalaemia, 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[1]
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea Common Vomiting, Abdominal pain upper	Common Diarrhoea, Vomiting, Nausea
Hepatobiliary Disorders	Very Common Abnormal liver function tests	Common Abnormal liver function tests
Skin and Subcutaneous Tissue Disorders	Very Common Rash, Dry skin	Common Rash, Pruritus
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms Common Myalgia, Musculoskeletal pain	
General Disorders and Administration Site Conditions	Very Common Fatigue, Asthenia, Pyrexia	Common Fatigue, Asthenia

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

Tabulated summary for combination therapy in MM
Table 2: ADRs reported in clinical trials in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Very Common Pneumonia, Upper respiratory tract infection, Bacterial, Viral and fungal infections (including opportunistic infections), Nasopharyngitis, Pharyngitis, Bronchitis Common Sepsis, Sinusitis	Common Pneumonia, Bacterial, Viral and fungal infections (including opportunistic infections), Sepsis, Bronchitis
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	Uncommon Basal cell carcinoma, Squamous skin cancer[^,*]	Common Acute myeloid leukaemia, Myelodysplastic syndrome, Squamous cell carcinoma of skin[**] Uncommon T-cell type acute leukaemia, Basal cell carcinoma, Tumour lysis syndrome
Blood and Lymphatic System Disorders	Very Common Neutropenia[^], Thrombocytopenia[^], Anemia, Haemorrhagic disorder[^], Leucopenias Common Febrile neutropenia, Pancytopenia Uncommon Haemolysis, Autoimmune haemolytic anemia, Haemolytic anemia	Very Common Neutropenia[^], Thrombocytopenia[^], Anemia, Leucopenias Common Febrile neutropenia[^], Pancytopenia, Haemolytic anemia Uncommon Hypercoagulation, Coagulopathy
Immune System Disorders	Uncommon Hypersensitivity[^]	
Endocrine Disorders	Common Hypothyroidism	
Metabolism and Nutrition Disorders	Very Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Decreased appetite, Weight decreased Common Hypomagnesaemia, Hyperuricaemia, Dehydration	Common Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Diabetes mellitus, Hypophosphataemia, Hyponatraemia, Hyperuricaemia, Gout, Decreased appetite, Weight decreased
Psychiatric Disorders	Very Common Depression, Insomnia Uncommon Loss of libido	Common Depression, Insomnia
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^	Common Respiratory distress, Dyspnoea
Gastrointestinal Disorders	Very Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting, Dyspepsia Common Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)[^], Dry mouth, Stomatitis, Dysphagia Uncommon Colitis, Caecitis	Common Diarrhoea, Constipation, Abdominal pain, Nausea, Vomiting
Hepatobiliary Disorders	Common Abnormal liver function tests Uncommon Hepatic failure[^]	Common Cholestasis, Abnormal liver function tests Uncommon Hepatic failure[^]
Skin and Subcutaneous Tissue Disorders	Very Common Rashes, Pruritus Common Urticaria, Hyperhidrosis, Dry skin, Skin hyperpigmentation, Eczema, Erythema Uncommon Skin discolouration, Photosensitivity reaction	Common Rashes
Musculoskeletal and Connective Tissue Disorders	Very Common Muscle spasms, Bone pain, Musculoskeletal and connective tissue pain and discomfort, Arthralgia Common Muscular weakness, Joint swelling, Myalgia	Common Muscular weakness, Bone pain Uncommon Joint swelling
Renal and Urinary Disorders	Very Common Renal failure (including acute) Common Haematuria[^], Urinary retention, Urinary incontinence Uncommon Acquired Fanconi syndrome	Uncommon Renal tubular necrosis
Reproductive System and Breast Disorders	Common Erectile dysfunction	
General Disorders and Administration Site Conditions	Very Common Fatigue, Oedema (including peripheral oedema), Pyrexia, Asthenia, Influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache and rigors) Common Chest pain, Lethargy	Common Fatigue, Pyrexia, Asthenia
Investigations	Common C-reactive protein increased	
Injury, Poisoning and Procedural Complications	Common Fall, Contusion[^]	

[^] See section 4.8 description of selected adverse reactions
[*] Squamous skin cancer was reported in clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls
[**] Squamous cell carcinoma of skin was reported in a clinical trial in newly diagnosed myeloma patients with lenalidomide/dexamethasone compared to controls

Tabulated summary of post-marketing adverse reactions
Table 3: ADRs reported in post-marketing use in patients treated with lenalidomide

System Organ Class/Preferred Term	All ADRs/Frequency	Grade 3-4 ADRs/Frequency
Infections and Infestations	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation	Not known Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Rare Tumour lysis syndrome
Blood and Lymphatic System Disorders	Not known Acquired haemophilia	
Immune System Disorders	Rare Anaphylactic reaction[^] Not known Solid organ transplant rejection Acute graft-versus-host disease (following allogeneic hematopoietic transplant)	Rare Anaphylactic reaction[^]
Endocrine Disorders	Common Hyperthyroidism	
Respiratory, Thoracic and Mediastinal Disorders	Uncommon Pulmonary hypertension	Rare Pulmonary hypertension Not known Interstitial pneumonitis
Gastrointestinal Disorders		Not known Pancreatitis, Gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)[^]
Hepatobiliary Disorders	Not known Acute hepatic failure[^], Hepatitis toxic[^], Cytolytic hepatitis[^], Cholestatic hepatitis[^], Mixed cytolytic/cholestatic hepatitis[^]	Not known Acute hepatic failure[^], Hepatitis toxic[^]
Skin and Subcutaneous Tissue Disorders		Uncommon Angioedema Rare Stevens-Johnson Syndrome[^], Toxic epidermal necrolysis[^] Not known Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms[^]

[^] See section 4.8 description of selected adverse reactions

Description of selected adverse reactions
Teratogenicity
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. In monkeys, lenalidomide induced malformations similar to those described with thalidomide. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

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

Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 4 neutropenia compared to placebo maintenance. Treatment-emergent AEs of neutropenia leading to lenalidomide discontinuation were reported. Grade 4 febrile neutropenia was reported at similar frequencies in the lenalidomide maintenance arms compared to placebo maintenance.
Lenalidomide maintenance after ASCT is associated with a higher frequency of grade 3 or 4 thrombocytopenia compared to placebo maintenance.

- 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. Grade 4 febrile neutropenia was observed infrequently.
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.

- 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. Grade 4 febrile neutropenia episodes were observed infrequently.
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia.

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 and severe skin reactions
Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of lenalidomide. A possible cross-reaction between lenalidomide and thalidomide has been reported.
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.

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).

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.

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 Pharmacodynamics properties
Pharmacotherapeutic group: Immunomodulating agent. 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.

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 drug 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 pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug 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 drug is undetectable in semen of a healthy subject 3 days after stopping the substance.
Biotransformation and elimination
In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A.
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 recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and patients with multiple myeloma. Pharmacokinetics analyses in patients with impaired renal function indicate that as renal function decreases (<50 mL/min), the total drug clearance decreases proportionally resulting in an increase in AUC. 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule content
Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate
Capsule shell 5 mg
Gelatin, Titanium dioxide, Yellow iron oxide, Red iron oxide, Black iron oxide, FD&C blue #1, FD&C yellow #6
Capsule shell 10 mg
Gelatin, Purified water, Titanium dioxide, Yellow iron oxide, Black iron oxide
Capsule shell 15 mg
Gelatin, Water, Titanium dioxide, Yellow iron oxide, Red iron oxide, Black iron oxide
Capsule shell 25 mg
Gelatin, Purified water, Titanium dioxide
Printing ink
Shellac, Propylene glycol, Strong ammonia solution, Potassium hydroxide, Black iron oxide

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Please refer to the outer carton

6.4 Storage condition
Store below 30ºC.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
The capsules are packed in PVC/ACLAR/ALU blister pack with leaflet inserted
Pack size of 21 capsules per carton box (3 blisters x 7 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. Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule.
Unused medicinal product should be returned to the pharmacist.

7. MANUFACTURER
Lotus Pharmaceutical Co., Ltd. Nantou Plant.
No. 30, Chenggong 1st Rd., Sinsing Village, Nantou City, Nantou County 54066, Taiwan

8. PRODUCT REGISTRATION HOLDER
Lotus Healthcare Malaysia Sdn. Bhd.
UOA Business Park, Tower 3
9th Floor, K03-09-11
1 Jalan Pengaturcara U1/51A, Section U1
40150 Shah Alam, Malaysia

9. DATE OF REVISION OF THE TEXT
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