LENMID Capsules (Lenalidomide)

Black Box Warning: Embryo-Fetal Toxicity, Hematologic Toxicity, And Venous Thromboembolism

Embryo-Fetal Toxicity
Do not use Lenalidomide during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting Lenalidomide treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after Lenalidomide treatment.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)
Lenalidomide can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q Myelodysplastic Syndromes (MDS) had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous Thromboembolism
Lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with Multiple Myeloma (MM) who were treated with Lenalidomide and dexamethasone therapy. 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, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with Lenalidomide may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

Composition

LENMID 5 Capsules
Each hard gelatin capsule contains:
Lenalidomide ....... 5 mg
Approved colours used in capsule shell
LENMID 10 Capsules
Each hard gelatin capsule contains:
Lenalidomide ....... 10 mg
Approved colours used in capsule shell
LENMID 25 Capsules
Each hard gelatin capsule contains:
Lenalidomide ........ 25 mg
Approved colours used in capsule shell

Dosage Form
Oral capsule

Pharmacology

Pharmacodynamics
Mechanism of Action
The mechanism of action of lenalidomide has not been fully characterized. Its activity is attributed to anti-neoplastic, immunomodulatory and anti-angiogenic properties.
It inhibits the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines from the peripheral mononuclear blood cells, and also inhibits the growth of Namalwa (human B cell lymphoma) and KG-1 (human myeloblastic) cells, with deletion of chromosome 5.
It inhibits the growth of MM cells, by inducing cell cycle arrest and apoptosis.
It inhibits, in vitro, the expression of cyclooxygenase-2 (COX-2).

Pharmacokinetics
Absorption
Lenalidomide is rapidly absorbed after oral administration, with a $T_{\text{max}}$ of 0.625-1.5 hours in healthy volunteers. Pharmacokinetic data in MDS patients is not available.
The $C_{\text{max}}$ is reduced by about 36%, when the drug is taken with food; however, the AUC remains unchanged. The pharmacokinetics of lenalidomide is linear. The $C_{\text{max}}$ and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose regimen does not result in drug accumulation.

Distribution
Lenalidomide is about 30% protein-bound.

Metabolism and Excretion
The metabolic profile of lenalidomide in humans has not been studied. Two-thirds of the drug is eliminated unchanged through urinary excretion in healthy volunteers. The elimination half-life is approximately 3 hours.

Special Populations
Renal Impairment
Clinical data are not available in MDS patients. However, in MM patients with mild renal impairment, the AUC increased by 56% when compared to that of healthy volunteers. Lenalidomide is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

Hepatic Impairment
Clinical data are not available.

Geriatric
Lenalidomide has been used in de15q MDS clinical trials in patients up to 95 years of age. The overall frequency of adverse events was the same in patients over 65 years of age as in younger patients; however, the frequency of serious
adverse events was higher in patients over 65 years of age. 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.

**Paediatric**
Clinical data are not available in patients below the age of 16 years.

**Gender**
The effects of gender on the pharmacokinetics of lenalidomide have not been studied.

**Race**
Clinical data are not available.

### Indications

**MM**
LENMID Capsules in combination with dexamethasone is indicated for the treatment of patients with MM who have received at least one prior therapy.

**MDS**
LENMID Capsules is indicated for the treatment of patients with transfusion-dependent anaemia due to low-or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

### Dosage And Administration

LENMID Capsules should be taken at about the same time each day. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. 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.

**MM**
The recommended starting dose of LENMID Capsules is 25 mg once daily on days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg once daily on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first four cycles of therapy and then 40 mg once daily orally on days 1-4 every 28 days. Treatment is continued or modified, based upon clinical and laboratory findings. Prescribing physicians should carefully evaluate as to which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

**Dose Adjustments for Haematologic Toxicities during MM Treatment**
Dose modification guidelines, as summarized below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia or other grade 3 or 4 toxicity, which are judged to be related to lenalidomide.

### Table 1: Platelet Counts: Thrombocytopenia in MM

<table>
<thead>
<tr>
<th>When Platelets</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When Neutrophils | Recommended Course
--- | ---
Fall to <1,000/mcL | Interrupt LENMID Capsules treatment, add G-CSF*, do a CBC count weekly.

Return to ≥1,000/mcL and neutropenia is the only toxicity | Resume LENMID Capsules at 25 mg daily.

Return to ≥1,000/mcL and if other toxicity | Resume LENMID Capsules at 15 mg daily.

Table 2: ANC: Neutropenia in MM
For each subsequent drop <1,000/mcL

<table>
<thead>
<tr>
<th>For each subsequent drop &lt;1,000/mcL</th>
<th>Interrupt LENMID Capsules treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to ≥1,000/mcL</td>
<td>Resume LENMID Capsules at 5 mg less than the previous dose. Do not dose below 5 mg daily.</td>
</tr>
</tbody>
</table>

In case of neutropenia, the physician should consider the use of growth factors in patient management.

*Granulocyte colony-stimulating factor

Other Grade 3/4 Toxicities in MM

For other grade 3/4 toxicities judged to be related to LENMID Capsules, hold treatment and restart at the next lower dose level when toxicity has resolved to ≤grade 2.

MDS

The recommended starting dose of LENMID Capsules is 10 mg daily. Treatment is continued or modified based upon clinical and laboratory findings.

Dose Adjustments During Treatment

Given below is the dose modification guideline for those who experience thrombocytopenia or neutropenia with lenalidomide treatment.

Table 3: Recommended Lenalidomide Dose Adjustment in Patients with Treatment-Related Thrombocytopenia
<table>
<thead>
<tr>
<th>Time to Thrombocytopenia</th>
<th>Baseline Value</th>
<th>When Platelets</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 4 weeks of starting therapy with 10 mg daily</td>
<td>≥1,00,000/mcL</td>
<td>Fall to</td>
<td>Interrupt LENMID treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Return to ≥50,000/mcL</td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt;1,00,000/mcL</td>
<td>Fall to 50% of baseline</td>
<td>Interrupt LENMID treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If baseline ≥60,000/mcL and returns to ≥50,000/mcL</td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If baseline returns to ≥30,000/mcL</td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td>After 4 weeks of starting treatment with 10 mg daily</td>
<td>platelet transfusions</td>
<td></td>
<td>Interrupt LENMID therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Return to ≥30,000/mcL (without haemostatic failure)</td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td>While on treatment with 5 mg daily</td>
<td>platelet transfusions</td>
<td></td>
<td>Interrupt LENMID therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Return to ≥30,000/mcL (without haemostatic failure)</td>
<td>Resume LENMID at 2.5 mg every other day</td>
</tr>
</tbody>
</table>

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Table 4: Recommended Lenalidomide Dose Adjustment in Patients with Treatment-Related Neutropenia
<table>
<thead>
<tr>
<th>Time to Neutropenia</th>
<th>Baseline Value</th>
<th>When Neutrophils</th>
<th>Recommended Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 4 weeks of starting therapy with 10 mg daily</td>
<td>≥1,000/mcL</td>
<td>Fall to</td>
<td>Interrupt LENMID treatment</td>
</tr>
<tr>
<td></td>
<td>Return to ≥1,000/ mcL</td>
<td></td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt;1,000/ mcL</td>
<td>Fall to</td>
<td>Interrupt LENMID therapy</td>
</tr>
<tr>
<td></td>
<td>Return to ≥500/mcL</td>
<td></td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td>After 4 weeks of starting treatment with 10 mg daily</td>
<td>days, or associated with fever (≥38.5oC)</td>
<td></td>
<td>Interrupt LENMID therapy</td>
</tr>
<tr>
<td></td>
<td>Return to ≥500/ mcL</td>
<td></td>
<td>Resume LENMID at 5 mg daily</td>
</tr>
<tr>
<td>While on treatment with 5 mg daily</td>
<td>7 days or associated with lever (≥38.5oC)</td>
<td></td>
<td>Interrupt LENMID therapy</td>
</tr>
<tr>
<td></td>
<td>Return to ≥500/ mcL</td>
<td></td>
<td>Resume LENMID at 2.5 mg every other day</td>
</tr>
</tbody>
</table>

Other Grade 3/4 Toxicities in MDS
For other grade 3/4 toxicities judged to be related to lenalidomide, hold treatment and restart at the 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 or toxic epidermal necrolysis is suspected, and should not be resumed following discontinuation from these reactions.
Discontinuation of lenalidomide
Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dl rise in haemoglobin, should discontinue lenalidomide treatment.
Starting Dose for Renal Impairment in MM, MDS
Since Lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of Lenalidomide are
recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, Lenalidomide starting dose adjustment is recommended for patients with CLcr

Table 5: Starting Dose Adjustments for Patients with Renal Impairment in MM, MDS or MCL

<table>
<thead>
<tr>
<th>Category</th>
<th>Renal Function (Cockcroft-Gault)</th>
<th>Dose in MM or MCL</th>
<th>Dose in MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Renal Impairment</td>
<td>CLcr 30-60 mL/min</td>
<td>Every 24 hours</td>
<td>5 mg Every 24 hours</td>
</tr>
<tr>
<td>Severe Renal Impairment</td>
<td>CLcr &lt; 30 mL/min (not requiring dialysis)</td>
<td>Every 48 hours</td>
<td>2.5 mg Every 24 hours</td>
</tr>
<tr>
<td>End Stage Renal Disease</td>
<td>CLcr &lt; 30 mL/min (requiring dialysis)</td>
<td>5 mg Once daily. On dialysis days, administer the dose following dialysis.</td>
<td>2.5 mg Once daily. On dialysis days, administer the dose following dialysis.</td>
</tr>
</tbody>
</table>

After initiation of Lenalidomide therapy, subsequent Lenalidomide dose modification is based on individual patient treatment tolerance, as described elsewhere.

Special Population

Paediatric Use
The safety and efficacy of lenalidomide in children aged 0-17 years has not yet been established. No data are available.

Geriatric Use
The effects of age on the pharmacokinetics of lenalidomide have not been studied. Lenalidomide has been used in clinical trials in MM patients up to 86 years of age. The percentage of patients aged 65 years 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 the greater pre-disposition of older individuals cannot be ruled out. 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.

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

Pregnancy Category X
Lenalidomide can cause fetal harm when administered to a pregnant female. Limb abnormalities were seen in the offspring of monkeys that were dosed with lenalidomide during organogenesis. This effect was seen at all doses tested. Due to the results of this developmental monkey study, and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Allergic Reactions
Lenalidomide is contraindicated in patients who have demonstrated a hypersensitivity (e.g. angio-oedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.
Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Warnings And Precautions

Drug Interactions
Results from human in vitro metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome (CY) P450 pathway, suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in humans.
in vitro studies demonstrate that lenalidomide is not a substrate of multidrug resistance proteins, MRP1, MRP2 or MRP3, nor a substrate of organic anion and cation uptake transporters, OAT1, OAT3, OATP1B1 or OCT1.
in vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

Digoxin
When digoxin was co-administered with multiple doses of lenalidomide (10 mg/day) the digoxin C_{max} and AUC_{0-infinity} were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgement and based on standard clinical practice in patients receiving this medication, is recommended during the administration of lenalidomide.

Warfarin
Co-administration of multiple-dose lenalidomide (10 mg) with single-dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of prothrombin time (PT) and International Normalized Ratio (INR) were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin.

Concomitant Therapies That May Increase the Risk of Thrombosis
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as oestrogen-containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone.
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in MM patients receiving lenalidomide with dexamethasone.

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 drugs, 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.

Interactions with other medicines
Co-administration of lenalidomide, a P-gp substrate, with known P-gp inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, quinidine, verapamil) may increase its plasma levels and thus its toxicity. If such a combination is to be given, patients should be closely monitored for the occurrence of side-effects.

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with drugs that inhibit cytochrome P450 enzymes is not likely to result in metabolic drug interactions in man. *in vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A.

Haematologic Toxicity
Lenalidomide can cause significant neutropenia and thrombocytopenia. Patients taking Lenalidomide for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients taking Lenalidomide for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients taking Lenalidomide for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction.

Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days).

In the pooled MM trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of Lenalidomide and dexamethasone than in patients treated with dexamethasone alone.

In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

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. Co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

Embryo-Fetal Toxicity
Lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning Lenalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with Lenalidomide, during therapy, during dose
interruptions and continuing for 4 weeks following discontinuation of Lenalidomide therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing Lenalidomide therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.

Males

Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking Lenalidomide and for up to 28 days after discontinuing Lenalidomide, even if they have undergone a successful vasectomy. Male patients taking Lenalidomide must not donate sperm.

Blood Donation

Patients must not donate blood during treatment with Lenalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to Lenalidomide.

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) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event).

In patients with myelodysplastic syndromes, treatment with lenalidomide monotherapy was also associated with a risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with multiple myeloma.

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.

Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single agent Lenalidomide therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the Lenalidomide treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92, consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred
more frequently in the Lenalidomide treatment arm. Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.

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

**Allergic Reactions**
Cases of allergic reaction/hypersensitivity reactions have been reported. 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**
Angio-oedema and serious dermatologic reactions, including SJS and TEN have been reported. These events can be fatal. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for grade 2-3 skin rash. Lenalidomide must be discontinued for angio-oedema, grade 4 rash, exfoliative or bullous rash or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions. Patients with a prior history of grade 4 rash associated with thalidomide treatment should not receive lenalidomide.

**Tumour Lysis Syndrome**
Fatal instances of tumour lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

**Tumour flare reaction**
Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Lenalidomide is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for tumor flare reaction (TFR) is recommended in patients with MCL. Tumor flare reaction may mimic progression of disease (PD). In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

**Hepatotoxicity**
Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination with dexamethasone: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic 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 side effects 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 medications known to be associated with liver dysfunction.

**Thyroid Function**
Cases of hypothyroidism have been reported and monitoring of thyroid function should be considered.

**Peripheral Neuropathy**
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.

**Lactose Intolerance**
Lenalidomide 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.

**Unused Capsules**
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

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

In clinical trials of newly diagnosed MM, a 4-fold increased incidence of SPMs has been observed in patients receiving lenalidomide (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of acute myeloid leukaemia (AML), Hodgkin lymphoma, MDS and solid tumours were observed in patients receiving lenalidomide in combination with melphalan or immediately following high-dose melphalan and autologous stem cell transplant (ASCT); cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received lenalidomide in the post-ASCT setting.

The risk of occurrence of SPMs 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 SPMs and institute treatment as indicated. When considering treatment with lenalidomide, both the potential benefit of lenalidomide and the risk of SPMs should be taken into account.

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

• **Karyotype**
  Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. In a clinical trial of Revlimid in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38.6%). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13.8%, compared to 17.3% for patients with Del (5q) and one additional cytogenetic abnormality. As a consequence, the benefit/risk ratio of Revlimid when MDS is associated with Del (5q) and complex cytogenetics is unknown.

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

**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*
• Premature ovarian failure confirmed by a specialist gynaecologist
• Previous bilateral salpingo-oophorectomy, or hysterectomy
• XY genotype, Turner syndrome, uterine agenesis.

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

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, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 contraceptive measures as soon as lenalidomide is dispensed following a negative pregnancy test
• She understands the need and accepts to undergo pregnancy testing 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. As a precaution, 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 1 week after dose interruptions and/or cessation of treatment.
• Understand that if his female partner becomes pregnant whilst he is taking Revlimid 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 one effective method of contraception for 4 weeks before therapy, during therapy, and until 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 dexamethasone, and to a lesser extent in patients with myelodysplastic syndromes 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 method 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 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 every 4 weeks, including 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.

Men

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 1 week after cessation of treatment if their partner is pregnant or of childbearing potential and not using effective contraception (even if the man has had a vasectomy).

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.

Patients should not donate blood during therapy or for 1 week 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 educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. 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.

Renal Impairment

Since lenalidomide is primarily excreted unchanged by the kidneys, adjustments to the starting dose of lenalidomide are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr

Hepatic Impairment

No study has been conducted in patients with hepatic impairment. The elimination of unchanged lenalidomide is predominantly by the renal route.

Pregnancy

Lenalidomide may cause foetal harm when administered to a pregnant woman. Due to the results of a developmental monkey study and lenalidomide's structural similarities to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Females of childbearing potential may be treated with lenalidomide, provided adequate precautions are taken to avoid pregnancy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g. hormonal contraception, tubal ligation, IUD or partner's vasectomy) and one additional effective method (e.g. latex condom, diaphragm or cervical cap), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of lenalidomide therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with lenalidomide must have pregnancy testing (sensitivity of at least 50 mIU/mL). The first test should be performed within 10-14 days and the second test within 24 hours prior to beginning lenalidomide therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counselling must be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs, lenalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

Safety and effectiveness in paediatric patients below the age of 18 have not been established.
Lenalidomide has been used in MM clinical trials in patients up to 86 years of age. Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were aged 65 years or over while 12% were aged 75 and over. The percentage of patients aged 65 years or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received lenalidomide/dexamethasone, 46% were aged 65 years and over. In both studies, patients >65 years of age were more likely than patients ≥65 years of age to experience DVT, PE, atrial fibrillation and renal failure following the use of lenalidomide. No differences in efficacy were observed between patients over 65 years of age and younger patients. Lenalidomide has been used in del 5q MDS clinical trials in patients up to 95 years of age. Of the 148 patients with del 5q MDS enrolled in the major study, 38% were aged 65 years and over, while 33% were aged 75 years and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% versus 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% versus 16%). No differences in efficacy were observed between patients over 65 years of age and younger patients. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Renal function should be monitored.

**Effects on the Ability to Drive and Use Machines**

Lenalidomide has a 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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

*Carcinogenicity:* Clinical data are not available.

*Mutagenesis:* Lenalidomide does not induce mutation.

*Fertility:* Animal studies did not reveal any parental toxicity and adverse effects of fertility and no parental toxicity. The effects of lenalidomide on reproduction have not been thoroughly assessed.

# Undesirable Effects

**Myelodysplastic syndromes**

The overall safety profile of Lenalidomide in patients with myelodysplastic syndromes is based on data from a total of 286 patients from one Phase II study and one Phase III study. In the Phase II, all 148 patients were on lenalidomide treatment. In the Phase III study, 69 patients were on lenalidomide 5 mg, 69 patients on lenalidomide 10 mg and 67 patients were on placebo during the double-blind phase of the study. Most adverse events tended to occur during the first 16 weeks of therapy with lenalidomide. Serious adverse reactions include:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia.

The most frequently observed adverse reactions which occurred more frequently in the lenalidomide groups compared to the control arm in the Phase III study were neutropenia (76.8%), thrombocytopenia (46.4%), diarrhea (34.8%), constipation (19.6%), nausea (19.6%), pruritus (25.4%), rash (18.1%), fatigue (18.1%) and muscle spasms (16.7%).
<table>
<thead>
<tr>
<th>System Organ Class/ Preferred Term</th>
<th>All Adverse Reactions/Frequency</th>
<th>Grade 3-4 Adverse Reactions/Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td>Pneumonia, upper respiratory tract infection Sepsis, bacterial, viral and fungal infections (including opportunistic infections), sinusitis, urinary tract infections</td>
<td>Pneumonia, bacterial, viral and fungal infections (including opportunistic infections)</td>
</tr>
<tr>
<td><strong>Neoplasms</strong></td>
<td>Basal cell carcinoma Squamous skin cancer*</td>
<td>Tumour lysis syndrome†</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Hypersensitivity*</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Hypothyroidism, hirsutism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Hypokalaemia, decreased appetite, anorexia Hypomagnesaemia, Hypocalcaemia Dehydration</td>
<td>Hypokalaemia, Hypocalcaemia, Hypophosphataemia</td>
</tr>
<tr>
<td><strong>Psychiatric Disorder</strong></td>
<td>Loss of libido, mood swings, hallucination</td>
<td>Depression</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysgeusia, headache, hypoaesthesia Ataxia, balance impaired</td>
<td>Cerebrovascular accident, dizziness, syncope Intracranial haemorrhage*, Transient ischaemic attack, Cerebral ischaemia</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Blurred vision</td>
<td>Cataract</td>
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<td>------------------------------------</td>
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<tr>
<td></td>
<td>Reduced visual acuity, cataract, cataract unilateral, ocular hypertension</td>
<td>Blindness</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Deafness (including hypoacusis), tinnitus</td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Atrial fibrillation, Bradycardia, Arrhythmia, QT prolongation, atrial flutter, ventricular extrasystoles, angina pectoris</td>
<td>Myocardial infarction*, Atrial fibrillation, Congestive cardiac failure, Tachycardia</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Venous thromboembolic events, predominantly DVT and PE* Hypotension Hypertension Ecchymosis</td>
<td>Venous thromboembolic events, predominantly DVT and PE* Ischaemia, peripheral ischaemia, intracranial venous sinus thrombosis</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Dyspnoea, Nasopharyngitis Pharyngitis, bronchitis, Epistaxis* Cough, hoarseness</td>
<td>Respiratory distress Interstitial pneumonitis†</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Constipation, diarrhoea, nausea, vomiting Gastrointestinal haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding), abdominal pain, dry mouth, stomatitis, dysphagia Colitis, caecitis, glossodynia</td>
<td>Diarrhoea, constipation, nausea Pancreatitis†</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>Abnormal Liver Function Tests Hepatic failure*, Acute hepatic failure†, Hepatitis toxic*, Cytolytic hepatitis†<em>, Cholestatic hepatitis†</em>, Mixed cytolytic/ cholestatic hepatitis††</td>
<td>Abnormal Liver Function Tests Hepatic failure*, Acute hepatic failure†, Hepatitis toxic††</td>
</tr>
</tbody>
</table>
### Skin and Subcutaneous Tissue Disorders
- **Rashes**: Urticaria, hyperhidrosis, dry skin, pruritus, skin hyperpigmentation, eczema, increased sweating, exanthem.
- **Skin discoloration** Photosensitivity reaction.

### Musculoskeletal and Connective Tissue Disorders
- **Muscle spasms**, bone pain, musculoskeletal and connective tissue pain and discomfort, back pain, pain in limb.
- **Joint swelling**

### Renal and Urinary Disorders
- **Haematuria**, urinary retention, urinary incontinence.
- **Acquired Fanconi syndrome**
- **Renal failure**
- **Renal tubular necrosis**

### Reproductive System and Breast Disorders
- **Erectile dysfunction**

### General Disorders and Administration Site Conditions
- **Fatigue**, oedema (including peripheral oedema), pyrexia, influenza-like illness syndrome (including pyrexia, myalgia, musculoskeletal pain, headache and rigors).
- **Chest pain**, lethargy, malaise.

### Injury, Poisoning and Procedural Complications
- **Contusion**

### Investigations
- Liver function tests abnormal, alanine aminotransferase increased, weight decreased.

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*†See Description of Selected Adverse Reactions*

*†Reports from postmarketing data*

Additionally, lenalidomide use in MDS can cause night sweats, erythema, rhinitis, asthenia, pain, rigors, arthralgia, myalgia, peripheral swelling, cellulitis, insomnia, dysuria, palpitations, granulocytopenia, multi-organ failure, hypoxia, pleural effusion, and splenic infarction.

In other clinical studies of lenalidomide in MDS patients, the following serious adverse events (regardless of relationship...
to the study drug treatment), not described in Table 7, were reported:

**Blood and Lymphatic System Disorders:** Warm-type haemolytic anaemia, splenic infarction, bone marrow depression, coagulopathy, haemolysis, haemolytic anaemia refractory anaemia.

**Cardiac Disorders:** Cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischaemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary oedema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction.

**Ear and Labyrinth Disorders:** Vertigo.

**Endocrine Disorders:** Basedow's disease.

**Gastrointestinal Disorders:** Gastrointestinal haemorrhage, colitis ischaemic, intestinal perforation, rectal haemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastro-oesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, peri-rectal abscess, small intestinal obstruction, upper gastrointestinal haemorrhage.

**General Disorders and Administration Site Conditions:** Disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death.

**Hepatobiliary Disorders:** The following hepatic disorders have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

**Immune System Disorders:** Hypersensitivity.

**Infections and Infestations:** Infection bacteraemia, central line infection, clostridial infection, ear infection Enterobacter sepsis, fungal infection herpes viral infection NOS (Not otherwise specified), influenza, kidney infection Klebsiella sepsis, lobar pneumonia, localized infection, oral infection, Pseudomonas infection, septic shock, sinusitis acute sinusitis, Staphylococcal infection, urosepsis.

**Injury, Poisoning and Procedural Complications:** Femur fracture, transfusion reaction, cervical vertebral fracture, femoral neck fracture, fractured pelvis, hip fracture, overdose, post-procedural haemorrhage, rib fracture, road traffic accident, spinal compression fracture.

**Investigations:** Blood creatinine increased, haemoglobin decreased, liver function tests abnormal, troponin-I increased.

**Metabolism and Nutrition Disorders:** Dehydration, gout, hypernatraemia, hypoglycaemia.

**Musculoskeletal and Connective Tissue Disorders:** Arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate.

**Neoplasms Benign, Malignant and Unspecified:** Acute leukaemia, AML, bronchoalveolar carcinoma, lung cancer metastatic, lymphoma, prostate cancer metastatic.

**Nervous System Disorders:** Cerebrovascular accident, aphasia, cerebellar infarction, cerebral infarction, depressed level of consciousness, dysarthria, migraine, spinal cord compression, subarachnoid haemorrhage, transient ischaemic attack.

**Psychiatric Disorders:** Confusional state.

**Renal and Urinary Disorders:** Renal failure, haematuria, renal failure acute, azotaemia, calculus ureteric, renal mass.

**Reproductive System and Breast Disorders:** Pelvic pain.

**Respiratory, Thoracic and Mediastinal Disorders:** Bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnoea exacerbated, interstitial lung disease, lung infiltration, wheezing.

**Skin and Subcutaneous Tissue Disorders:** Acute febrile neutrophilic dermatosis.

**Vascular System Disorders:** DVT, hypotension, aortic disorder, ischaemia, thrombophlebitis superficial, thrombosis.

**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**

The combination of lenalidomide with dexamethasone in MM 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 MM 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**

The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with MM. Concomitant administration of erythropoietic agents or a 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**

SJS and TEN have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

**SPMs**

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

### Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide postmarketing experience with lenalidomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: allergic conditions (angio-oedema, SJS, TEN), tumour lysis syndrome and tumour flare reaction, pneumonitis, and transient abnormal liver laboratory tests.

### Overdosage

There is no specific experience in the management of lenalidomide overdose in patients; although, in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.

In studies, the dose-limiting toxicity was essentially haematological. In the event of overdose, supportive care is advised.
Incompatibility

Not applicable.

Shelf-Life

2 years

Storage And Handling Instructions

Store between 15°C & 30°C.
Care should be exercised in the handling of lenalidomide. Lenalidomide capsules should not be opened or crushed. If a powder from lenalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If Lenalidomide contacts the mucous membranes, flush thoroughly with water.
Procedures for the proper handling and disposal of anticancer drugs should be considered.

Packaging Information

LENMID 5 Capsules: Container pack of 10 Capsules
LENMID 10 Capsules: Container pack of 10 Capsules
LENMID 25 Capsules: Container pack of 10 Capsules

Last updated: November 2013
Last reviewed: November 2013

LENMID Capsules

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