For the use of a Registered Medical Practitioner

NOJETOR 10/25
(Lenalidomide Capsules 10 mg and 25 mg)

COMPOSITION

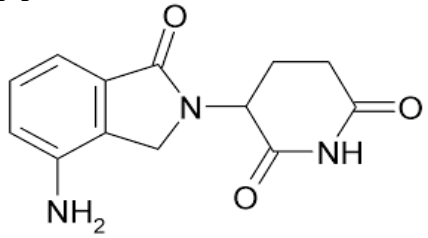
Each Capsule contains:
Lenalidomide.....10 mg
Approved colours used in Capsule shell.

Each Capsule contains:
Lenalidomide.....25 mg
Approved colours used in Capsule shell

Warning: Lenalidomide should never be taken by pregnant women or women capable of becoming pregnant as even a single dose can cause severe birth defects or death to an unborn baby.

DESCRIPTION

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

CLINICAL PHARMACOLOGY

Mechanism of action

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties. Lenalidomide inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including multiple myeloma, mantle cell lymphoma, and del (5q)

myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models including multiple myeloma. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In multiple myeloma cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

Pharmacodynamics
The effect of lenalidomide on the QTc interval in 60 healthy male subjects in a randomized, thorough QT study with placebo and positive controls revealed that at a dose two times the maximum recommended dose, lenalidomide does not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the mean differences between lenalidomide and placebo was below 10 ms.

Pharmacokinetic
Absorption
Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of lenalidomide in patients with MDS **(**Myelodysplastic Syndromes**)** the maximum plasma concentrations reported between 0.5 and 6 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Systemic exposure (AUC) of lenalidomide in MDS patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects.

Administration of a single 25 mg dose of lenalidomide with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in Cmax. In the trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism
Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

Elimination
Elimination is primarily renal. Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. 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.

The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MDS.

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

Patients with Renal Impairment
The reported study for pharmacokinetics of lenalidomide in patients with renal impairment due to nonmalignant conditions included 5 patients with mild renal impairment (creatinine clearance 57-74 mL/min), 6 patients with moderate renal impairment (creatinine clearance 33-46 mL/min), 6 patients with severe renal impairment (creatinine clearance 17-29 mL/min), and 6 patients with end stage renal disease requiring dialysis were administered a single oral 25-mg dose of lenalidomide. As a control group comparator, 7 healthy subjects of similar age with normal renal function (creatinine clearance 83-145 mL/min) were also administered a single oral 25-mg dose of lenalidomide. As creatinine clearance decreased from mild to severe impairment, half-life increased and drug clearance decreased linearly. Patients with moderate and severe renal impairment had a 3-fold increase in half-life and a 66% to 75% decrease in drug clearance compared to healthy subjects. Patients on hemodialysis (n=6) given a single, 25-mg dose of lenalidomide had an approximate 4.5-fold increase in half-life and an 80% decrease in drug clearance compared to healthy subjects. Approximately 40% of the administered dose was removed from the body during a single dialysis session.

Adjustment of the starting dose of lenalidomide is recommended in patients with moderate or severe (CLcr < 60 mL/min) renal impairment and in patients on dialysis.

Elderly Patients
No dedicated clinical studies have been conducted to evaluate pharmacokinetics of lenalidomide in the elderly. Reported population pharmacokinetic analyses included patients with ages ranging from 39 to 85 years old and showed that age does not influence the disposition of lenalidomide.

Patients with Hepatic Disease
Reported population pharmacokinetic analyses included patients with mild hepatic impairment (N = 16, total bilirubin >1 to ≤ 1.5 x ULN or AST > ULN) and showed that mild hepatic impairment does not influence the disposition of lenalidomide. There are no data available for patients with moderate to severe hepatic impairment.

Pediatric
No pharmacokinetic data are available in patients below the age of 18 years.

Other Intrinsic Factors

Reported population pharmacokinetic analyses show that body weight (33-135 kg), gender, race, and type of hematological malignancies (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients.

INDICATION

For the treatment of patients with transfusion dependent anemia due to low or intermediate -1-risk myelodysplastic syndrome (MDS) associated with deletion 5q cytogenic abnormality with or without additional cytogenic abnormalities.

DOSE AND METHOD OF ADMINISTRATION

Myelodysplastic Syndromes

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

Dose adjustments for hematologic toxicities during MDS treatment

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

Platelet counts

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ≥100,000/mcL	
When Platelets	**Recommended Course**
Fall to <50,000/mcL	Interrupt lenalidomide treatment
Return to ≥50,000/mcL	Resume lenalidomide at 5 mg daily
If baseline <100,000/mcL	
When Platelets	**Recommended Course**
Fall to 50% of the baseline value	Interrupt lenalidomide treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume lenalidomide at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume lenalidomide at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL with platelet transfusions	Interrupt lenalidomide treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume lenalidomide at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily in MDS

When Platelets	**Recommended Course**
<30,000/mcL or <50,000/mcL	Interrupt lenalidomide treatment

with platelet transfusions Return to ≥30,000/mcL (without hemostatic failure)	Resume lenalidomide at 2.5 mg daily

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

Absolute Neutrophil counts (ANC)

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily in MDS

If baseline ANC ≥1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <750/mcL Return to ≥1,000/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg daily
If baseline ANC <1,000/mcL	
When Neutrophils	**Recommended Course**
Fall to <500/mcL Return to ≥500/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C) Return to ≥500/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily in MDS

When Neutrophils	**Recommended Course**
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C) Return to ≥500/mcL	Interrupt lenalidomide treatment Resume lenalidomide at 2.5 mg daily

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 physician's discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

Starting Dose for Renal Impairment in 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 reported pharmacokinetic study in patients with renal impairment due to non-malignant conditions, lenalidomide starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with

creatinine clearances less than 7 mL/min have not been studied. The recommendation for initial starting doses for patients with MDS is as follows:

Table 1: Starting Dose Adjustments for Patients with Renal Impairment in MDS

Category	Renal Function (Cockcroft-Gault)	Dose in MDS
Moderate Renal Impairment	CLcr 30-60 mL/min	5 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	2.5 mg Every 24 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	2.5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification is based on individual patient treatment tolerance.

CONTRAINDICATION

Pregnancy

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 hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide.

WARNINGS AND PRECAUTIONS

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. Reported 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.

Hematologic Toxicity

Lenalidomide can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medication that may increase risk of bleeding. Patients taking lenalidomide should have their complete blood counts assessed periodically as described below.

Patients taking lenalidomide for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. 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).

Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboses are increased in patients treated with lenalidomide. A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in patients with multiple myeloma after at least one prior therapy who were treated with REVLIMID and dexamethasone therapy compared to patients treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all patients received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT Arms,

respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT Arms (3.8%, 2.8%, and 3.7%, respectively).

Myocardial infarction (1.7%) and stroke (CVA) (2.3%) are increased in patients with multiple myeloma after at least one prior therapy who were treated with lenalidomide and dexamethasone therapy compared to patients treated with placebo and dexamethasone (0.6%, and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT Arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT Arms (0.8%, 0.6 %, and 0.6%, respectively). Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g. hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in patients with refractory and relapsed multiple myeloma who were treated with lenalidomide and dexamethasone compared to 8.3% thrombosis in patients treated with placebo and dexamethasone. The median time to first thrombosis event was 2.8 months. In the NDMM study in which nearly all patients received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% in patients in the combined Rd Continuous and Rd18 Arms, and was 11.6% in the MPT Arm. The median time to first thrombosis event was 4.37 months in the combined Rd Continuous and Rd18 Arms. Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving lenalidomide.

Increased Mortality in Patients with CLL (chronic lymphocytic leukemia)
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 [95% CI: 1.08 – 3.41], 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.

Second Primary Malignancies
In clinical trials in patients with multiple myeloma receiving lenalidomide an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM patients receiving lenalidomide in combination with oral melphalan (frequency of 5.3%) or immediately following high dose intravenous melphalan and autologous stem cell transplantation (ASCT) (frequency of up to

5.2%). The frequency of AML and MDS cases in the lenalidomide/dexamethasone arms was observed to be 0.4%. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting.

Patients who received lenalidomide-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration lenalidomide-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

Hepatotoxicity
Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Preexisting viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Allergic Reactions
Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 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 angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

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

Tumor Flare Reaction
Tumor flare reaction has been reported 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.

Impaired Stem Cell Mobilization
A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported. In patients who are (ASCT) candidates, referral to a transplant center should occur early in treatment to optimize the timing of the stem cell collection. In patients who received more than 4 cycles of a lenalidomide-containing treatment or for whom inadequate numbers of CD 34+ cells have been collected with GCSF alone, G-CSF with cyclophosphamide or the combination of G-CSF with a CXCR4 inhibitor may be considered.

DRUG INTERACTIONS
Results from human in vitro studies show that lenalidomide is neither metabolized by nor inhibit or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.

In vitro studies reported that lenalidomide is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

Digoxin
As reported, when digoxin was co-administered with multiple doses of lenalidomide (10 mg/day) the digoxin Cmax and $AUC_{0-\infty}$ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of lenalidomide.

Warfarin
As reported, co-administration of multiple doses 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 PT and 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 multiple myeloma 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 estrogen containing therapies, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category X

Risk Summary

Lenalidomide can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Lenalidomide is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. 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 a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Animal data

In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre-and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

Nursing mothers

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.

Pediatric use
Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric use
Lenalidomide has been used in clinical trials in patients up to 86 years of age. No differences in efficacy were reported 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. Monitor renal function.

Females of Reproductive Potential and Males
Lenalidomide can cause fetal harm when administered during pregnancy. Females of reproductive potential must avoid pregnancy 4 weeks before therapy, while taking lenalidomide, during dose interruptions and for at least 4 weeks after completing therapy.

Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed. Females of reproductive potential must have 2 negative pregnancy tests before initiating lenalidomide. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing lenalidomide. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

Males
Lenalidomide is present in the semen of males who take lenalidomide. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide, during dose interruptions 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.

Renal Impairment
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 (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis.

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

ADVERSE EFFECTS

- Embryo-Fetal Toxicity
- Neutropenia and thrombocytopenia
- Venous and arterial thromboembolism
- Increased Mortality in Patients with CLL
- Second Primary Malignancies
- Hepatotoxicity
- Allergic Reactions
- Tumor lysis syndrome
- Tumor flare reactions

Because clinical trials are reported under widely varying conditions, adverse reaction rates reported in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Multiple Myeloma
Data evaluation report from 703 patients in two studies who received at least one dose of lenalidomide/dexamethasone (353 patients) or placebo/dexamethasone (350 patients).

In the lenalidomide/dexamethasone treatment group, 269 patients (76%) underwent at least one dose interruption with or without a dose reduction of lenalidomide compared to 199 patients (57%) in the placebo/dexamethasone treatment group. Of these patients who had one dose interruption with or without a dose reduction, 50% in the lenalidomide /dexamethasone treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group. Most adverse events and Grade 3/4 adverse events were more frequent in patients who received the combination of lenalidomide/dexamethasone compared to placebo/dexamethasone.

Tables 2,3 and 4 summarize the adverse reactions reported for lenalidomide /dexamethasone and placebo/dexamethasone groups.

Table: 2 Adverse Reactions Reported in ≥5% of Patients and with a ≥2% Difference in Proportion of Patients Between the lenalidomide /dexamethasone and Placebo/dexamethasone Groups

System Organ Class/ Preferred Term	lenalidomide/Dex* (n=353) n (%)	Placebo/Dex * (n=350) n (%)
Blood and lymphatic system disorders		
Neutropenia %	149 (42.2)	22 (6.3)
Anemia [@]	111 (31.4)	83 (23.7)
Thrombocytopenia [@]	76 (21.5)	37 (10.6)
Leukopenia	28 (7.9)	4 (1.1)
Lymphopenia	19 (5.4)	5 (1.4)
General disorders and administration site conditions		
Fatigue	155 (43.9)	146 (41.7)
Pyrexia	97 (27.5)	82 (23.4)
Peripheral edema	93 (26.3)	74 (21.1)
Chest Pain	29 (8.2)	20 (5.7)
Lethargy	24 (6.8)	8 (2.3)
Gastrointestinal disorders		
Constipation	143 (40.5)	74 (21.1)
Diarrhea[@]	136 (38.5)	96 (27.4)
Nausea [@]	92 (26.1)	75 (21.4)
Vomiting [@]	43 (12.2)	33 (9.4)
Abdominal Pain [@]	35 (9.9)	22 (6.3)
Dry Mouth	25 (7.1)	13 (3.7)
Musculoskeletal and connective tissue disorders		
Muscle cramp	118 (33.4)	74 (21.1)

Back pain	91 (25.8)	65 (18.6)
Bone Pain	48 (13.6)	39 (11.1)
Pain in Limb	42 (11.9)	32 (9.1)
Muscle cramp	118 (33.4)	74 (21.1)
Nervous system disorders		
Dizziness	82 (23.2)	59 (16.9)
Tremor	75 (21.2)	26 (7.4)
Dysgeusia	54 (15.3)	34 (9.7)
Hypoaesthesia	36 (10.2)	25 (7.1)
Neuropathy [a]	23 (6.5)	13 (3.7)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	83 (23.5)	60 (17.1)
Nasopharyngitis	62 (17.6)	31 (8.9)
Pharyngitis	48 (13.6)	33 (9.4)
Bronchitis	40 (11.3)	30 (8.6)
Infections[b] and infestations		
Upper respiratory tract infection	87 (24.6)	55 (15.7)
Pneumonia [@]	48 (13.6)	29 (8.3)
Urinary Tract Infection	30 (8.5)	19 (5.4)
Sinusitis	26 (7.4)	16 (4.6)
Skin and subcutaneous system disorders		
Rash [c]	75 (21.2)	33 (9.4)
Sweating Increased	35 (9.9)	25 (7.1)
Dry Skin	33 (9.3)	14 (4.0)

Pruritus	27 (7.6)	18 (5.1)
Metabolism and nutrition disorders		
Anorexia	55 (15.6)	34 (9.7)
Hypokalemia	48 (13.6)	21 (6.0)
Hypocalcemia	31 (8.8)	10 (2.9)
Appetite Decreased	24 (6.8)	14 (4.0)
Dehydration	23 (6.5)	15 (4.3)
Hypomagnesaemia	24 (6.8)	10 (2.9)
Investigations		
Weight Decreased	69 (19.5)	52 (14.9)
Eye disorders		
Blurred vision	61 (17.3)	40 (11.4)
Vascular disorders		
Deep vein thrombosis [%]	33 (9.3)	15 (4.3)
Hypertension	28 (7.9)	20 (5.7)
Hypotension	25 (7.1)	15 (4.3)

Table 3: Grade 3/4 Adverse Reactions Reported in ≥2% Patients and With a ≥1% Difference in Proportion of Patients Between the lenalidomide /dexamethasone and Placebo/dexamethasone groups

System Organ Class/ Preferred Term	**lenalidomide/Dex* (n=353) n (%)**	**Placebo/Dex * (n=350) n (%)**
Blood and lymphatic system disorders		
Neutropenia [%]	118 (33.4)	12 (3.4)
Thrombocytopenia [@]	43 (12.2)	22 (6.3)
Anemia [@]	35 (9.9)	20 (5.7)

Leukopenia	14 (4.0)	1 (0.3)
Lymphopenia	10 (2.8)	4 (1.1)
Febrile Neutropenia [%]	8 (2.3)	0 (0.0)
General disorders and administration site conditions		
Fatigue	23 (6.5)	17 (4.9)
Vascular disorders		
Deep vein thrombosis [%]	29 (8.2)	12 (3.4)
Infections[b] and infestations		
Pneumonia [@]	30 (8.5)	19 (5.4)
Urinary Tract Infection	5 (1.4)	1 (0.3)
Metabolism and nutrition disorders		
Hypokalemia	17 (4.8)	5 (1.4)
Hypocalcemia	13 (3.7)	6 (1.7)
Hypophosphatemia	9 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism[@]	14 (4.0)	3 (0.9)
Respiratory Distress [@]	4 (1.1)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Muscle weakness	20 (5.7)	10 (2.9)
Gastrointestinal disorders		
Diarrhea [@]	11 (3.1)	4 (1.1)
Constipation	7 (2.0)	1 (0.3)
Nausea [@]	6 (1.7)	2 (0.6)
Cardiac disorders		

Atrial fibrillation [@]	13 (3.7)	4 (1.1)
Tachycardia	6 (1.7)	1 (0.3)
Cardiac Failure Congestive [@]	5 (1.4)	1 (0.3)
Nervous System disorders		
Syncope	10 (2.8)	3 (0.9)
Dizziness	7 (2.0)	3 (0.9)
Eye Disorders		
Cataract	6 (1.7)	1 (0.3)
Cataract Unilateral	5 (1.4)	0 (0.0)
Psychiatric Disorder		
Depression	10 (2.8)	6 (1.7)

Table 4: Serious Adverse Reactions Reported in ≥1% Patients and With a ≥1% Difference in Proportion of Patients Between the lenalidomide /dexamethasone and placebo / dexamethasone Groups

System Organ Class/ Preferred Term	**lenalidomide/Dex* (n=353) n (%)**	**Placebo/Dex * (n=350) n (%)**
Blood and lymphatic system disorders		
Febrile Neutropenia[%]	6 (1.7)	0 (0.0)
Vascular disorders		
Deep vein thrombosis[%]	26 (7.4)	11 (3.1)
Infections[b] and infestations		
Pneumonia [@]	33 (9.3)	21 (6.0)
Respiratory, thoracic, and mediastinal disorders		
Pulmonary embolism[@]	13 (3.7)	3 (0.9)
Cardiac disorders		

Atrial fibrillation [@]	11 (3.1)	2 (0.6)
Cardiac Failure Congestive [@]	5 (1.4)	0 (0.0)
Nervous system disorders		
Cerebrovascular accident [@]	7 (2.0)	3 (0.9)
Gastrointestinal disorders		
Diarrhea [@]	6 (1.7)	2 (0.6)
Musculoskeletal and connective tissue disorders		
Bone Pain	4 (1.1)	0 (0.0)

For all tables above:
n – Number of Patients
* -All Treatment Emergent AEs with ≥5% of Patients in lenalidomide / Dex and at Least 2% Difference in Proportion between the Two Arms (Safety population)
# -All Treatment Emergent Grades 3 and 4 AEs with ≥1% Patients in lenalidomide / Dex and at Least 1% Difference in Proportion between the Two Arms -(Safety population)
& -All Treatment Emergent Serious AEs with ≥1% Patients in lenalidomide / Dex and at Least 1% Difference in Proportion between the Two Arms -(Safety population)
@ -ADRs with Death as an outcome
% -ADRs which were considered to be life threatening (if the outcome of the event was death, it is included with death cases)
[a] -All PTs under the MedDRA SMQ of Neuropathy of a peripheral sensory nature will be considered listed
[b] -All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
c -All PTs under HLT of Rash will be considered listed
Dex=dexamethasone
Median duration of exposure among patients treated with lenalidomide /dexamethasone was 44 weeks while median duration of exposure among patients treated with placebo/dexamethasone was 23 weeks. This should be taken into consideration when comparing frequency of adverse events between two treatment groups lenalidomide /dexamethasone vs. placebo/dexamethasone.

Venous and Arterial Thromboembolism
Deep vein thrombosis (DVT) was reported as a serious (7.4%) or severe (8.2%) adverse drug reaction at a higher rate in the lenalidomide/dexamethasone group compared to 3.1 % and 3.4% in the placebo/dexamethasone group, respectively. Discontinuations due to DVT adverse reactions were reported at comparable rates between groups.

Pulmonary embolism (PE) was reported as a serious adverse drug reaction including Grade 3/4 (3.7%) at a higher rate in the lenalidomide/dexamethasone group compared to 0.9% in the placebo/dexamethasone group. Discontinuations due to PE adverse reactions were reported at comparable rates between groups.

Myocardial infarction was reported as a serious (1.7%) or severe (1.7%) adverse drug reaction at a higher rate in the lenalidomide/dexamethasone group compared to 0.6 % and 0.6% respectively in the placebo/dexamethasone group. Discontinuation due to MI (including acute) adverse reactions was 0.8% in lenalidomide/dexamethasone group and none in the placebo/dexamethasone group.

Stroke (CVA) was reported as a serious (2.3%) or severe (2.0%) adverse drug reaction in the lenalidomide/dexamethasone group compared to 0.9% and 0.9% respectively in the placebo/dexamethasone group. Discontinuation due to stroke (CVA) was 1.4% in lenalidomide/ dexamethasone group and 0.3% in the placebo/dexamethasone group.

Other Adverse Reactions
In reported clinical studies of lenalidomide in patients with multiple myeloma, the following adverse drug reactions (ADRs) not described above that occurred at ≥1% rate and of at least twice of the placebo percentage rate were reported:

Blood and lymphatic system disorders: pancytopenia, autoimmune hemolytic anemia

Cardiac disorders: bradycardia, myocardial infarction, angina pectoris

Endocrine disorders: hirsutism

Eye disorders: blindness, ocular hypertension

Gastrointestinal disorders: gastrointestinal hemorrhage, glossodynia

General disorders and administration site conditions: malaise

Investigations: liver function tests abnormal, alanine aminotransferase increased

Nervous system disorders: cerebral ischemia

Psychiatric disorders: mood swings, hallucination, loss of libido

Reproductive system and breast disorders: erectile dysfunction

Respiratory, thoracic and mediastinal disorders: cough, hoarseness

Skin and subcutaneous tissue disorders: exanthem, skin hyperpigmentation

Clinical Trials Experience in Myelodysplastic Syndromes
In reported study a total of 148 patients received at least 1 dose of 10 mg lenalidomide in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10 mg starting dose of lenalidomide. The most frequently reported adverse events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative site conditions.

Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events. The next most common adverse events observed were diarrhea (48.6%; 72/148), pruritus (41.9%; 62/148), rash (35.8%; 53/148) and fatigue (31.1%; 46/148). Table 1 summarizes the adverse events that were reported in ≥ 5% of the lenalidomide treated patients in the del 5q MDS clinical study. Table 2 summarizes the most frequently observed Grade 3 and Grade 4 adverse reactions regardless of relationship to treatment with lenalidomide. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 5: Summary of Adverse Events Reported in ≥5% of the LENALIDOMIDE Treated Patients in del 5q MDS Clinical Study

System organ class/Preferred term [a]	**10 mg Overall** (N=148)
Patients with at least one adverse event	148 (100.0)
Blood and Lymphatic System Disorders	
Thrombocytopenia	91 (61.5)
Neutropenia	87 (58.8)
Anemia	17 (11.5)
Leukopenia	12 (8.1)
Febrile Neutropenia	8 (5.4)
Skin and Subcutaneous Tissue Disorders	
Pruritus	62 (41.9)
Rash	53 (35.8)
Dry Skin	21 (14.2)
Contusion	12 (8.1)
Night Sweats	12 (8.1)
Sweating Increased	10 (6.8)
Ecchymosis	8 (5.4)
Erythema	8 (5.4)
Gastrointestinal Disorders	
Diarrhea	72 (48.6)
Constipation	35 (23.6)
Nausea	35 (23.6)

Abdominal Pain	18 (12.2)
Vomiting	15 (10.1)
Abdominal Pain Upper	12 (8.1)
Dry Mouth	10 (6.8)
Loose Stools	9 (6.1)
Respiratory, Thoracic and Mediastinal Disorders	34 (23.0)
Nasopharyngitis	29 (19.6)
Cough	25 (16.9)
Dyspnea	23 (15.5)
Pharyngitis	22 (14.9)
Epistaxis	10 (6.8)
Dyspnea Exertional	10 (6.8)
Rhinitis	9 (6.1)
Bronchitis	
General Disorders and Administration Site Conditions	
Fatigue	46 (31.1)
Pyrexia	31 (20.9)
Edema Peripheral	30 (20.3)
Asthenia	22 (14.9)
Edema	15 (10.1)
Pain	10 (6.8)
Rigors	9 (6.1)
Chest Pain	8 (5.4)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	32 (21.6)
Back Pain	31 (20.9)
Muscle Cramp	27 (18.2)
Pain in Limb	16 (10.8)
Myalgia	13 (8.8)
Peripheral Swelling	12 (8.1)
Nervous System Disorders	
Dizziness	29 (19.6)
Headache	29 (19.6)
Hypoesthesia	10 (6.8)
Dysgeusia	9 (6.1)
Peripheral Neuropathy	8 (5.4)

Infections and Infestations	
Upper Respiratory Tract Infection	22 (14.9)
Pneumonia	17 (11.5)
Urinary Tract Infection	16 (10.8)
Sinusitis	12 (8.1)
Cellulitis	8 (5.4)
Metabolism and Nutrition Disorders	
Hypokalemia	16 (10.8)
Anorexia	15 (10.1)
Hypomagnesemia	9 (6.1)
Investigations	12 (8.1)
Alanine Aminotransferase Increased	
Psychiatric Disorders	
Insomnia	15 (10.1)
Depression	8 (5.4)
Renal and Urinary Disorders	
Dysuria	10 (6.8)
Vascular Disorders	
Hypertension	9 (6.1)
Endocrine Disorders	
Acquired Hypothyroidism	10 (6.8)
Cardiac Disorders	
Palpitations	8 (5.4)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 6: Most Frequently Observed Grade 3 and 4 Adverse Events [1] Regardless of Relationship to Study Drug Treatment

Preferred term [2]	**10 mg (N=148)**
Patients with at least one Grade 3/4 AE	131 (88.5)
Neutropenia	79 (53.4)
Thrombocytopenia	74 (50.0)
Pneumonia	11 (7.4)
Rash	10 (6.8)

Anemia	9 (6.1)
Leukopenia	8 (5.4)
Fatigue	7 (4.7)
Dyspnea	7 (4.7)
Back Pain	7 (4.7)
Febrile Neutropenia	6 (4.1)
Nausea	6 (4.1)
Diarrhea	5 (3.4)
Pyrexia	5 (3.4)
Sepsis	4 (2.7)
Dizziness	4 (2.7)
Granulocytopenia	3 (2.0)
Chest Pain	3 (2.0)
Pulmonary Embolism	3 (2.0)
Respiratory Distress	3 (2.0)
Pruritus	3 (2.0)
Pancytopenia	3 (2.0)
Muscle Cramp	3 (2.0)
Respiratory Tract Infection	2 (1.4)
Upper Respiratory Tract Infection	2 (1.4)
Asthenia	2 (1.4)
Multi-organ Failure	2 (1.4)
Epistaxis	2 (1.4)
Hypoxia	2 (1.4)
Pleural Effusion	2 (1.4)
Pneumonitis	2 (1.4)
Pulmonary Hypertension	2 (1.4)
Vomiting	2 (1.4)
Sweating Increased	2 (1.4)
Arthralgia	2 (1.4)
Pain in Limb	2 (1.4)
Headache	2 (1.4)
Syncope	2 (1.4)

[1] Adverse events with frequency ≥1% in the 10 mg Overall group. Grade 3 and 4 are based on National Cancer Institute Common Toxicity Criteria version 2.
[2] Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred Term category.

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

Blood and lymphatic system disorders: warm type hemolytic anemia, splenic infarction, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia, refractory anemia

Cardiac disorders: cardiac failure congestive, atrial fibrillation, angina pectoris, cardiac arrest, cardiac failure, cardio-respiratory arrest, cardiomyopathy, myocardial infarction, myocardial ischemia, atrial fibrillation aggravated, bradycardia, cardiogenic shock, pulmonary edema, supraventricular arrhythmia, tachyarrhythmia, ventricular dysfunction

Ear and labyrinth disorders: vertigo

Endocrine disorders: Basedow's disease

Gastrointestinal disorders: gastrointestinal hemorrhage, colitis ischemic, intestinal perforation, rectal hemorrhage, colonic polyp, diverticulitis, dysphagia, gastritis, gastroenteritis, gastroesophageal reflux disease, obstructive inguinal hernia, irritable bowel syndrome, melena, pancreatitis due to biliary obstruction, pancreatitis, perirectal abscess, small intestinal obstruction, upper gastrointestinal hemorrhage

General disorders and administration site conditions: disease progression, fall, gait abnormal, intermittent pyrexia, nodule, rigors, sudden death

Hepatobiliary disorders: hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure

Immune system disorders: hypersensitivity

Infections and infestations infection bacteremia, central line infection, clostridial infection, ear infection, *Enterobacter* sepsis, fungal infection, herpes viral infection NOS, 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 hemorrhage, rib fracture, road traffic accident, spinal compression fracture

Investigations: blood creatinine increased, hemoglobin decreased, liver function tests abnormal, troponin I increased

Metabolism and nutrition disorders: dehydration, gout, hypernatremia, hypoglycemia

Musculoskeletal and connective tissue disorders: arthritis, arthritis aggravated, gouty arthritis, neck pain, chondrocalcinosis pyrophosphate

Neoplasms benign, malignant and unspecified: acute leukemia, acute myeloid leukemia, 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 hemorrhage, transient ischemic attack

Psychiatric disorders: confusional state

Renal and urinary disorders: renal failure, hematuria, renal failure acute, azotemia, calculus ureteric, renal mass

Reproductive system and breast disorders: pelvic pain

Respiratory, thoracic and mediastinal disorders: bronchitis, chronic obstructive airways disease exacerbated, respiratory failure, dyspnea exacerbated, interstitial lung disease, lung infiltration, wheezing

Skin and subcutaneous tissue disorders: acute febrile neutrophilic dermatosis

Vascular system disorders: deep vein thrombosis, hypotension, aortic disorder, ischemia, thrombophlebitis superficial, thrombosis

Clinical Trials Experience in Mantle Cell Lymphoma
In the MCL trial, a total of 134 patients received at least 1 dose of lenalidomide. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 3 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with lenalidomide. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

Table 7: Incidence of Adverse Reactions (≥10%) or Grade 3 / 4 AE (in at least 2 patients) in Mantle Cell Lymphoma

System organ class/Preferred term	**All AEs[1] (N=134) N (%)**	**Grade 3/4 AEs[2] (N=134) N (%)**
General disorders and administration site conditions		

Fatigue	45 (3 4)	9 (7)
Pyrexia[$]	31 (23)	3 (20
Edema peripheral	21 (16)	0
Asthenia [$]	19 (14)	4 (3)
General physical health deterioration	3 (2)	2 (1)
Gastrointestinal disorders		
Diarrhea[$]	42 (31)	8 (6)
Nausea[$]	40 (30)	1 (<1)
Constipation	21 (16)	1 (<1)
Vomiting[$]	16 (12)	1 (<1)
Abdominal pain[$]	13 (10)	5 (4)
Musculoskeletal and Connective tissue disorders		
Back Pain	18 (13)	2 (1)
Muscle spasms	17 (13)	1 (<1)
Arthralgia	11 (8)	2 (1)
Muscular weakness[$]	8 (6)	2 (1)
Respirator, thoracic and mediastinal disorder		
Cough	38 (28)	1 (<1)
Dyspnea[$]	24 (18)	8 (6)
Pleural Effusion	10 (7)	2 (1)
Hypoxia	3 (2)	2 (1)
Pulmonary embolism	3 (2)	2 (1)
Respiratory distress[$]	2 (1)	2 (1)
Oropharyngeal pain	13 (10)	0
Infection and infestation		
Pneumonia[@$]	19 (14)	12 (9)
Upper respiratory tract infection	17 (13)	0
Cellulitis[$]	3 (2)	2 (1)
Bacteremia[$]	2 (1)	2 (1)
Staphylococcal sepsis[$]	2 (1)	2 (1)
Urinary tract infection[$]	5 (4)	2 (1)
Skin and subcutaneous tissue disorders		
Rash [+]	30 (22)	2 (1)
Pruritus	23 (17)	1 (<1)
Blood and lymphatic system disorders		
Neutropenia	65 (49)	58 (43)
Thrombocytopenia[%$]	48 (36)	37 (28)
Leukopenia[$]	41 (31)	15 (11)
Leukopenia[$]	20 (15)	9 (7)
Lymphopenia	10 (7)	5 (4)
Febrile neutropenia[$]	8 (6)	8 (6)
Metabolism and nutrition disorder		
Decrease appetite	19 (14)	1 (<1)

Hypokalemia	17 (13)	3 (2)
Dehydration[$]	10 (7)	4 (3)
Hypocalcemia	4 (3)	2 (1)
Hyponatremia	3 (2)	3 (2)
Renal and urinary disorder		
Renal failure[$]	5 (4)	2 (1)
Vascular disorder		
Hypotension[@$]	9 (7)	4 (3)
Deep vein thrombosis[$]	5 (4)	5 (4)
Neoplasms benign, malignant and unspecified (incl cysts and polyp)		
Tumor flare	13 (10)	0
Squamous cell carcinoma of skin[$]	4 (3)	4 (3)
Investigations		
Weight decreased	17 (13)	0

MCL trial AEs – All treatment emergent AEs with >10% of subjects

[2]-MCL trial Grade 3/4 AEs – All treatment-emergent Grade 3/4 AEs in 2 or more subjects

[$]-MCL trial Serious AEs – All treatment-emergent SAEs in 2 or more subjects

[@]-AEs where at least one resulted in a fatal outcome

[%]-AEs where at least one was considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)

[#]-All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed

[+]-All PTs under HLT of Rash will be considered listed

The following adverse events which have occurred in other indications and not described above have been reported (5-10%) in patients treated with lenalidomide monotherapy for mantle cell lymphoma.

General disorders and administration site conditions: Chills

Musculoskeletal and connective tissue disorders: Pain in extremity

Nervous system disorders: Dysguesia, headache, neuropathy peripheral

Infections and infestations: Respiratory tract infection, sinusitis, nasopharyngitis

Skin and subcutaneous tissue disorders: Dry skin, night sweats

The following serious adverse events not described above and reported in 2 or more patients treated with lenalidomide monotherapy for mantle cell lymphoma.

Respiratory, Thoracic and Mediastinal Disorders: Chronic obstructive pulmonary disease

Infections and Infestations: Clostridium difficile colitis, sepsis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Basal cell carcinoma

Cardiac Disorder: Supraventricular tachycardia

Postmarketing Experience
The following adverse drug reactions have been identified from the worldwide post-marketing experience with enalidomide: Allergic conditions (angioedema, SJS, TEN), tumor lysis syndrome (TLS) and tumor flare reaction (TFR), pneumonitis, hepatic failure, including fatality, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis and transient abnormal liver laboratory tests. 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.

Cases of hypothyroidism and hyperthyroidism have also been reported. Optimal control of thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

OVERDOSE
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 hematological. In the event of overdose, supportive care is advised.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store below 25º excursions permitted up to 30ºC, Protect from light. Keep out of reach of children.

PRESENTATIONS
Nojetor 10/25 is available in HDPE Bottle of 30 Capsules.

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