

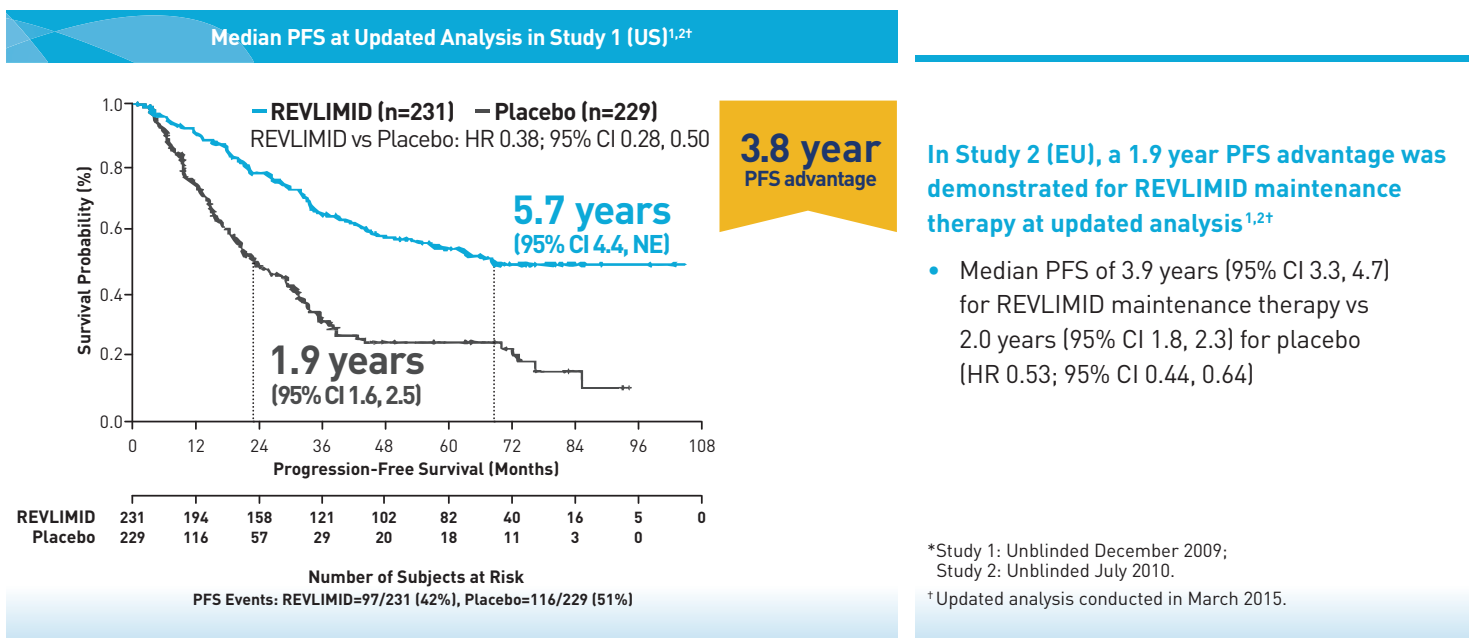
March 2017

**Celgene Corporation is pleased to announce the new approval for the use of REVLIMID<sup>®</sup> (lenalidomide) as maintenance therapy for MM patients after autologous hematopoietic stem cell transplantation (auto-HSCT)**

REVLIMID is indicated as maintenance therapy in patients with multiple myeloma (MM) following autologous hematopoietic stem cell transplantation (auto-HSCT). REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials

**REVLIMID maintenance therapy extended progression-free survival (PFS) vs placebo in two pivotal studies**

- In Study 1 (US), median PFS at unblinding\* was 2.8 years for REVLIMID vs 1.6 years for placebo (HR 0.38; 95% CI 0.27, 0.54;  $P < 0.001$ )
- In Study 2 (EU), median PFS at unblinding\* was 3.4 years for REVLIMID vs 1.9 years for placebo (HR 0.50; 95% CI 0.39, 0.64;  $P < 0.001$ )



**Trial Design:** Study 1 (US; enrolled patients aged 18-70 years) and Study 2 (EU; enrolled patients aged <65 years) were multicenter, randomized 1:1, double-blind, parallel-group, placebo-controlled studies conducted in newly diagnosed patients who received auto-HSCT after induction therapy within 12 months. The primary endpoint for both studies was PFS defined from randomization to the date of progression or death, whichever occurred first. Patients were randomized to REVLIMID or placebo within 90-100 days post-transplant and 90-180 days post-transplant in Studies 1 and 2, respectively. Patients needed at least a stable disease response following hematologic recovery, and must have had CrCl  $\geq 30$  mL/min. Patients in the placebo arm of Study 1 were allowed to cross over to receive REVLIMID before disease progression; patients in Study 2 were not recommended to cross over. Please see Prescribing Information for full patient demographics. In both studies, starting dose was REVLIMID 10 mg once daily on Days 1-28 of repeated 28-day cycles. If tolerated, dose could be increased to 15 mg once daily after 3 months in the absence of dose-limiting toxicity, and treatment was to be continued until disease progression or patient withdrawal for another reason. Dose was reduced, interrupted, and/or discontinued as needed to manage toxicities. A dose increase to 15 mg once daily occurred in 135 patients (58%) in Maintenance Study 1, and in 185 patients (60%) in Maintenance Study 2.

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM**

**Embryo-Fetal Toxicity**  
Do not use REVLIMID 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 REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS<sup>®</sup> program.

REVLIMID is only available through a restricted distribution program, REVLIMID REMS<sup>®</sup>. Please see additional Important Safety Information throughout letter and accompanying full Prescribing Information, including Boxed WARNINGS.

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM (continued)**

Information about the REVLIMID REMS<sup>®</sup> program is available at [www.celgeneriskmanagement.com](http://www.celgeneriskmanagement.com) or by calling the manufacturer's toll-free number 1-888-423-5436.

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q 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 MDS 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 and Arterial Thromboembolism**

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

**ADVERSE REACTIONS**

The most frequently reported Grade 3 or 4 reactions in ≥20% (REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm. The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (5%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (55%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 21%).

**CONTRAINDICATIONS**

**Pregnancy:** REVLIMID can cause fetal harm when administered to a pregnant female and 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 risk to the fetus

**Allergic Reactions:** REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

**Dosing and Administration**



\*ANC ≥1000/mcL and/or platelet counts ≥75,000/mcL.

- The recommended starting dose of REVLIMID maintenance therapy is 10 mg once daily, dosed continuously on Days 1-28 of repeated 28-day cycles
- If tolerated, dose can be increased to 15 mg after 3 cycles
- REVLIMID should be continued until disease progression or unacceptable toxicity

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### Starting Dose for Renal Impairment for Maintenance Therapy in MM

The recommendations for starting doses for patients with renal impairment are as follows:

Starting Dose Adjustments for Patients with Renal Impairment	
Renal Function	Dose
CrCl 30-60 mL/min	5 mg once daily
CrCl <30 mL/min (not requiring dialysis)	2.5 mg once daily
CrCl <30 mL/min (requiring dialysis)	2.5 mg once daily On dialysis days, administer the dose following dialysis

- Base subsequent REVLIMID dose increase or decrease on individual patient treatment tolerance

### Important Dosing Information

- Capsules should not be opened, broken, or chewed
- Lenalidomide is primarily excreted unchanged by the kidney. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function
- Monitor CBCs every 7 days (weekly) for the first 2 cycles, on Days 1 and 15 of Cycle 3, and every 28 days (4 weeks) thereafter
- Treatment is continued or modified based on clinical and laboratory findings
- Dose modification guidelines are recommended to manage Grade 3/4 neutropenia or thrombocytopenia. For other Grade 3/4 toxicities judged to be related to lenalidomide, hold treatment and restart at next lower dose level when toxicity has resolved to ≤Grade 2
- Patients may require dose interruption and/or reduction
- Patients may require the use of blood product support and/or growth factors

### Dose Adjustments for Hematologic Toxicities

Summarized below are dose modification recommendations to manage Grade 3 or 4 neutropenia, thrombocytopenia, or other Grade 3 or 4 toxicities judged to be related to REVLIMID.

Grade 3/4 Neutropenia	
When Neutrophil Levels (ANC)	Recommended Course
Fall to <500/mcL	Interrupt and follow with weekly CBC
Return to ≥500/mcL	Resume at next lower dose continuously for Days 1 to 28 of repeated 28-day cycle
If at the 5 mg daily dose, for a subsequent drop to <500/mcL	Interrupt treatment*
Return to >500/mcL	Resume at 5 mg daily for Days 1 to 21 of 28-day cycle*

\*Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle.

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## Grade 3/4 Thrombocytopenia

When Platelet Levels	Recommended Course
Fall to <30,000/mcL	Interrupt REVLIMID treatment, follow CBC weekly
Return to ≥30,000/mcL	Resume REVLIMID at next lower dose, continuously for Days 1 to 28 of repeated 28-day cycle
If at the 5 mg daily dose, for each subsequent drop <30,000/mcL	Interrupt treatment*
Return to ≥30,000/mcL	Resume REVLIMID at 5 mg daily for Days 1 to 21 of 28-day cycle*

\*Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle.

### Important Information about REVLIMID REMS<sup>®</sup>

- REVLIMID can cause fetal harm when administered to a pregnant woman, and is contraindicated in pregnant females or females capable of becoming pregnant
- To avoid embryo-fetal exposure, REVLIMID is only available under a restricted distribution program called “REVLIMID Risk Evaluation and Mitigation Strategy”
- Prescribers and pharmacies certified with REVLIMID REMS<sup>®</sup> can prescribe and dispense the product to patients who are enrolled and meet all the conditions of the REVLIMID REMS<sup>®</sup> program
- Female patients of reproductive potential must use at least one highly effective method of contraception and at least one additional method, concurrently, every time they have sex with a male
- Female patients of reproductive potential must obtain 2 negative pregnancy tests prior to initiating therapy. The first test must be performed within 10-14 days, and the second within 24 hours, prior to prescribing REVLIMID. Subsequent pregnancy tests should occur weekly during the first 4 weeks, then every 4 weeks in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles
- If pregnancy does occur, REVLIMID must be immediately discontinued. Any suspected embryo-fetal exposure to REVLIMID must be reported immediately to the FDA via the MedWatch number at **1-800-FDA-1088** and also to the Celgene Customer Care Center at **1-888-423-5436**. The patient should be referred to an OB/GYN experienced in reproductive toxicity
- Male patients must be instructed to use a latex or synthetic condom every time they have sexual intercourse with a female of reproductive potential
- Male patients must be instructed not to donate sperm during treatment (including dose interruptions) and for 4 weeks after their last dose
- Counsel patients not to share REVLIMID capsules, and not to donate blood during treatment (including dose interruptions) and for 4 weeks after receiving their last dose
- Instruct patients not to extensively handle or open REVLIMID capsules
- Instruct patients to return unused REVLIMID capsules to Celgene, their REVLIMID prescriber, or their REVLIMID dispensing pharmacy for disposal

**REVLIMID is only available through a restricted distribution program, REVLIMID REMS<sup>®</sup>.**

**Please see additional Important Safety Information throughout letter and accompanying full Prescribing Information, including Boxed WARNINGS.**

## Important Safety Information (continued)

### WARNINGS AND PRECAUTIONS

#### Embryo-Fetal Toxicity: See Boxed WARNINGS

- Females of Reproductive Potential: See Boxed WARNINGS
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

**REVLIMID REMS<sup>®</sup> Program: See Boxed WARNINGS:** Prescribers and pharmacies must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements

**Hematologic Toxicity:** REVLIMID 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 medications that may increase risk of bleeding. **MM:** Patients taking REVLIMID/dex or REVLIMID as maintenance therapy should have their complete blood counts (CBC) assessed every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter

**Venous and Arterial Thromboembolism: See Boxed WARNINGS:** Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID. 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). Thromboprophylaxis is recommended and the regimen should be based on patient's underlying risks. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision

**Increased Mortality in Patients with CLL:** In a clinical trial in the first line treatment of patients with CLL, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

**Second Primary Malignancies (SPM):** In clinical trials in patients with MM receiving REVLIMID, an increase of hematologic plus solid tumor SPM, notably AML and MDS have been observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID/dex. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID 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 REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions. REVLIMID capsules contain lactose; risk-benefit of treatment should be evaluated in patients with lactose intolerance

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

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**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of lenalidomide for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion

**Impaired Stem Cell Mobilization:** A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection

**Thyroid Disorders:** Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function before start of REVLIMID treatment and during therapy

## ADVERSE REACTIONS

### Multiple Myeloma

- **Maintenance Therapy Post-Auto HSCT:** The most frequently reported Grade 3 or 4 reactions in ≥20% (REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm
- The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (5%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (55%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 21%)

## DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels is recommended due to increased C<sub>max</sub> and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dex and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin

## USE IN SPECIFIC POPULATIONS

- **PREGNANCY: See Boxed WARNINGS.** If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436
- **LACTATION:** There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID
- **PEDIATRIC USE:** Safety and effectiveness have not been established in pediatric patients
- **RENAL IMPAIRMENT:** Adjust the starting dose of REVLIMID based on creatinine clearance value and in patients on dialysis

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## Celgene Patient Support® Your single source for access support

Celgene Patient Support® provides patients with help accessing REVLIMID. Depending on the patient's insurance situation, there are programs and organizations that may help pay for their REVLIMID

- Celgene Commercial Co-pay Program for eligible patients with commercial or private insurance (including healthcare exchanges)\*
- Independent third-party organizations for patients who are unable to afford their medication (including patients with Medicare, Medicaid, or other government-sponsored insurance)†
- Celgene Patient Assistance Program (PAP) for qualified patients who are uninsured or underinsured‡

\*Other eligibility requirements and restrictions apply. Please see full Terms and Conditions at [celgenepatientsupport.com](http://celgenepatientsupport.com).

†Financial and medical eligibility requirements vary by organization.

‡Patients must meet specified financial and eligibility requirements to qualify for assistance.

There are 3 simple ways to enroll patients in Celgene Patient Support®

- Enroll online at [www.celgenepatientsupport.com](http://www.celgenepatientsupport.com)
- Call us at 1-800-931-8691, Monday – Thursday, 8 am – 7 pm ET, and Friday, 8 am – 6 pm ET (*translation services available*)
- E-mail or fax a completed enrollment form to [patientsupport@celgene.com](mailto:patientsupport@celgene.com) or fax 1-800-822-2496

## References

1. REVLIMID [package insert]. Summit, NJ: Celgene Corp; 2017.
2. Data on file. Celgene Corp; 2017.

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