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FDA Expands Indication for REVLIMID® (lenalidomide) as a Maintenance Treatment for Patients with Multiple Myeloma Following Autologous Hematopoietic Stem Cell Transplant (auto-HSCT)

REVLIMID is the first and only treatment approved for maintenance following auto-HSCT

Updated data from two large, randomized, controlled studies demonstrated median progression-free survival (PFS) advantages of 3.8 and 1.9 years, respectively, in favor of patients receiving REVLIMID compared to no maintenance

Median overall survival (OS) for patients receiving REVLIMID in each study was 9.3 years and 8.8 years, respectively, compared to 7 and 7.3 years for no maintenance in a descriptive analysis (studies not powered for OS)

Approval enables Celgene to provide patients with treatment options across the multiple myeloma spectrum

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) today announced that the U.S. Food and Drug Administration (FDA) has expanded the existing indication for REVLIMID (lenalidomide) 10 mg capsules to include use for patients with multiple myeloma as maintenance therapy following autologous hematopoietic stem cell transplant (auto-HSCT). The expanded indication makes REVLIMID the first and only treatment to receive FDA approval for maintenance use following auto-HSCT.

"Autologous stem cell transplant after induction therapy is part of the continuum of care for transplant-eligible multiple myeloma patients. However, most patients will still see their disease recur or progress after this treatment," said Philip McCarthy, M.D., Director, Blood and Marrow Transplant Center, Department of Medicine at Roswell Park Cancer Institute. "Lenalidomide maintenance therapy, which has been shown to increase progression-free survival following autologous stem cell transplant in clinical trials can be considered a standard of care for these patients."

The approval was based on two large studies including more than 1,000 patients comparing REVLIMID maintenance therapy given until disease progression or unacceptable toxicity after auto-HSCT versus no maintenance. In both studies, the primary efficacy endpoint was progression-free survival (PFS) defined from randomization to the date of progression or death, whichever occurred first. In the most current PFS analysis, Study 1 (U.S.-based NCI sponsored cooperative group study CALGB 100104) demonstrated a median PFS of 5.7 years (95% CI: 4.4-not estimable) versus 1.9 years (95% CI: 1.6-2.5) for no maintenance, a difference of 3.8 years (HR 0.38 [95% CI: 0.28-0.50]). Study 2 (European-based study IFM 2005-02) also showed a benefit with a median PFS of 3.9 years (95% CI: 3.3-4.7) versus 2 years (95% CI: 1.8-2.3) for no maintenance, a difference of 1.9 years (HR 0.53 [95% CI: 0.44-0.64]). Individual studies were not powered for an overall survival endpoint. A descriptive analysis showed the median overall survival in Study 1 was 9.3 years (95% CI: 8.5-not estimable) for patients who received REVLIMID versus 7 years (95% CI: 5.9-8.6) for no maintenance (HR 0.59 [95% CI: 0.44-0.78]). In Study 2, median overall survival was 8.8 years (95% CI: 7.4-not estimable) for patients who received REVLIMID versus 7.3 years (95% CI: 6.7-9.0) for no maintenance (HR 0.90 [95% CI: 0.72-1.13]).

"In newly-diagnosed multiple myeloma, auto-HSCT remains a viable option for many patients and often provides a strong response against the disease," said Michael Pehl, President, Global Hematology and Oncology for Celgene. "By expanding the approval for REVLIMID to include post-transplant maintenance, patients have the potential to maintain those responses and, importantly, delay progression of the disease."

As described in the prescribing information, REVLIMID can cause fetal harm and is contraindicated in females who are pregnant. REVLIMID is only available through a restricted distribution program, Revlimid REMS®. Deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke occur in patients with MM treatment with REVLIMID and thromboprophylaxis is recommended. See additional Important Safety Information below.

The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2 respectively) 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%). The most frequently reported Grade 3 or 4 reactions (more than 20% in the REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia.

The frequencies of onset of adverse reactions were generally highest in the first six months of treatment and then the frequencies decreased over time or remained stable throughout treatment.

In patients receiving REVLIMID maintenance therapy, hematologic second primary malignancies (SPM) occurred in 7.5% of patients compared to 3.3% in patients receiving placebo. The incidence of hematologic plus solid tumor (excluding squamous cell carcinoma and basal cell carcinoma) SPM was 14.9%, compared to 8.8% in patients receiving placebo with a median follow-up of 91.5 months. Non-melanoma skin cancer SPM, including squamous cell carcinoma and basal cell carcinoma, occurred in 3.9% of patients receiving REVLIMID maintenance, compared to 2.6% in the placebo arm. Patients should be monitored for the development of second primary malignancies. Take into account both the potential benefit of REVLIMID and the risk of second primary malignancies when considering treatment with REVLIMID.

REVLIMID in combination with dexamethasone was previously approved in June 2006 for use in patients with multiple myeloma who have received at least one prior therapy, and the indication expanded in February 2015 to include patients newly diagnosed with multiple myeloma.

In June 2016, an application was submitted to the European Medicines Agency (EMA) for the review of REVLIMID as maintenance treatment in NDMM patients after receiving an autologous stem cell transplant. In January 2017, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the use of REVLIMID as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who have undergone autologous stem cell transplantation.

About CALGB 100104 (Study 1)

CALGB 100104 was a phase III, randomized, controlled, double-blind, multi-center study conducted in 47 centers by the CALGB, which is now part of the Alliance for Clinical Trials in Oncology, a US national oncology cooperative group. 460 newly diagnosed multiple myeloma patients - aged between 18 and 70 years (CLcr ≥ 30 mL/min) - who had undergone induction therapy within 12 months of diagnosis and achieved at least stable disease (SD) or better 90-100 days following autologous stem cell transplant (ASCT), were randomized to receive either REVLIMID maintenance or placebo. The REVLIMID maintenance dose was 10 mg/day (after 3 months increased to 15 mg/day if tolerated) until disease progression, intolerable side effects, patient withdrawal for another reason, or death. The dose was reduced, or treatment was temporarily interrupted or stopped, as needed to manage toxicity. A dose increase to 15 mg once daily occurred in 135 patients (58%).

About IFM 2005-02 (Study 2)

IFM 2005-02 was a phase III, controlled, double-blind, multi-center study conducted by the University Hospital of Toulouse in concert with the IFM, an independent French myeloma cooperative group, at 78 centers in France, Belgium, and Switzerland. 614 newly diagnosed multiple myeloma patients younger than 65 years (CLcr ≥ 30 mL/min) who had undergone induction therapy and did not present with signs of disease progression within 6 months of undergoing ASCT. Patients were then randomized to receive a two-month consolidation regimen of REVLIMID monotherapy 25 mg per day on 21/28 days, followed by either REVLIMID maintenance or placebo. The REVLIMID dose was 10 mg/day (after 3 months increased to15 mg/day if tolerated) until disease progression, intolerable side effects, patient withdrawal for another reason or death. The dose was reduced, or treatment was temporarily interrupted or stopped, as needed to manage toxicity. A dose increase to 15 mg once daily occurred in 185 patients (60%).

About REVLIMID®

REVLIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of patients with multiple myeloma (MM)

REVLIMID is indicated as maintenance therapy in patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT)

REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

REVLIMID® is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has

relapsed or progressed after two prior therapies, one of which included bortezomib

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials

Important Safety Information

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® program).

Information about the REVLIMID REMS® program is available at 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.

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

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® 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 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. **MDS:** 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 dose reduction. Please see the **Black Box WARNINGS** for further information. **MCL:** Patients taking REVLIMID for MCL should have their CBCs 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

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

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

- **In newly diagnosed:** The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more Grade 3 and 4 and serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18
- The most common adverse reactions reported in ≥20% (Arm Rd Continuous): diarrhea (46%), anemia (44%), neutropenia (35%), fatigue (33%), back pain (32%), asthenia (28%), insomnia (28%), rash (26%), decreased appetite (23%), cough (23%), dyspnea (22%), pyrexia (21%), abdominal pain (21%), muscle spasms (20%), and thrombocytopenia (20%)
- **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%)
- **After at least one prior therapy:** The most common adverse reactions reported in ≥20% (REVLIMID/dex vs dex/placebo): fatigue (44% vs 42%), neutropenia (42% vs 6%), constipation (41% vs 21%), diarrhea (39% vs 27%), muscle cramp (33% vs 21%), anemia (31% vs 24%), pyrexia (28% vs 23%), peripheral edema (26% vs 21%), nausea (26% vs 21%), back pain (26% vs 19%), upper respiratory tract infection (25% vs 16%), dyspnea (24% vs 17%), dizziness (23% vs 17%), thrombocytopenia (22% vs 11%), rash (21% vs 9%), tremor (21% vs 7%), and weight decreased (20% vs 15%)

Myelodysplastic Syndromes

- Grade 3 and 4 adverse events reported in ≥ 5% of patients with del 5q MDS were neutropenia (53%), thrombocytopenia (50%), pneumonia (7%), rash (7%), anemia (6%), leukopenia (5%), fatigue (5%), dyspnea (5%), and back pain (5%)
- Adverse events reported in ≥15% of del 5q MDS patients (REVLIMID): thrombocytopenia (61.5%), neutropenia (58.8%), diarrhea (49%), pruritus (42%), rash (36%), fatigue (31%), constipation (24%), nausea (24%), nasopharyngitis (23%), arthralgia (22%), pyrexia (21%), back pain (21%), peripheral edema (20%), cough (20%), dizziness (20%), headache (20%), muscle cramp (18%), dyspnea (17%), pharyngitis (16%), epistaxis (15%), asthenia (15%), upper respiratory tract infection (15%)

Mantle Cell Lymphoma

- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%)
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%)

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} 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 the creatinine clearance value and for patients on dialysis

Please see full Prescribing Information, including Boxed WARNINGS.

About Celgene

Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global biopharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through next-generation solutions in protein homeostasis, immuno-oncology, epigenetics, immunology and neuro-inflammation. For more information, please visit www.celgene.com. Follow Celgene on Social Media: @Celgene, Pinterest, LinkedIn, Facebook and YouTube.

Forward-Looking Statements

This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook" and similar expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in our Annual Report on Form 10-K and our other reports filed with the Securities and Exchange Commission.

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