FDA APPROVES REVLIMID® (LENALIDOMIDE) IN COMBINATION WITH RITUXIMAB FOR THE TREATMENT OF ADULT PATIENTS WITH PREVIOUSLY TREATED FOLLICULAR LYMPHOMA OR MARGINAL ZONE LYMPHOMA

Approval marks the first chemotherapy-free combination regimen for patients who have relapsed or did not respond to previous treatment

Approval based on Phase 3 AUGMENT study, which showed the combination significantly improved median progression-free survival versus rituximab monotherapy

May 28, 2019 – Summit, N.J. – Celgene Corporation (NASDAQ: CELG) today announced the U.S. Food and Drug Administration (FDA) approved REVLIMID® (lenalidomide) in combination with a rituximab product (R²) for the treatment of adult patients with previously treated follicular lymphoma (FL) or marginal zone lymphoma (MZL) following Priority Review designation. This is the first FDA-approved combination treatment regimen for patients with these indolent forms of non-Hodgkin’s lymphoma (NHL) that does not include chemotherapy.

“Nearly 15 years following the initial FDA approval, REVLIMID continues to demonstrate benefits for new patient populations,” said Jay Backstrom, M.D., M.P.H., Chief Medical Officer for Celgene. “REVLIMID in combination with rituximab (R²) leads to immune-mediated treatment effects and represents a chemotherapy-free treatment option that can help patients with previously treated follicular lymphoma and marginal zone lymphoma delay disease progression.”

Immune dysfunction (meaning the immune system is not functioning optimally) is a defining aspect of indolent forms of NHL, including FL and MZL.1,2 When this dysfunction occurs, lymphocytes in the immune system either fail to detect or target cancerous cells.1,2

“Chemotherapy continues to be a standard of care for indolent forms of NHL, but most patients will relapse or become refractory to their current treatment,” said Meghan Gutierrez, Chief Executive Officer for the Lymphoma Research Foundation. “This approval represents a new therapeutic option for previously treated patients with follicular and marginal zone lymphomas, including those who relapse or no longer respond to initial treatment. We commend the patients and scientists who participated in the clinical study for advancing lymphoma research and treatment.”

The approval of R² is based primarily on results from the randomized, double-blind, Phase 3 AUGMENT study, which evaluated the efficacy and safety of the R² combination versus rituximab plus placebo in patients with previously treated FL (n=295) and MZL (n=63).

In the AUGMENT study, treatment with R² demonstrated a statistically significant improvement in the primary endpoint of progression-free survival (PFS), evaluated by an independent review committee, versus rituximab-placebo. The median PFS was 39.4 months for patients treated with R² and 14.1 months for those treated with rituximab-placebo (HR: 0.46; 95% CI, 0.34-0.62; P<0.0001). Median follow-up time was 28.3 months (range, 0.1-51.3) in the intent to treat population (n=358). Although not statistically
powered to detect a difference in overall survival, a numeric trend for improvement in overall survival (a secondary endpoint) was also seen with R² versus rituximab-placebo (16 vs. 26 deaths) (HR: 0.61; 95% CI, 0.33-1.13).

REVLIMID is only available through a restricted distribution program called REVLIMID REMS® program. REVLIMID has a boxed warning for embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism. Adverse reactions reported in ≥15% of patients with FL/MZL treated with R² were: neutropenia (58%), diarrhea (31%), constipation (26%), cough (24%), fatigue (22%), rash (22%), pyrexia (21%), leukopenia (20%), pruritus (20%), upper respiratory tract infections (18%), abdominal pain (18%), anemia (16%), headache (15%), thrombocytopenia (15%).

A Marketing Authorization Application for R² is currently under review by the European Medicines Agency for the treatment of relapsed/refractory FL and MZL. A supplemental new drug application was also submitted to the Japanese Pharmaceuticals and Medical Devices Agency for an additional indication as well as dosage and administration updates for lenalidomide in combination with rituximab for the treatment of relapsed/refractory indolent B-cell NHL.

About Indolent Lymphoma
Lymphoma is a blood cancer that develops in lymphocytes, a type of white blood cell in the immune system that helps protect the body from infection. There are two classes of lymphoma – Hodgkin’s lymphoma and non-Hodgkin’s lymphoma (NHL) – each with specific subtypes that determine how the cancer behaves, spreads and should be treated.

Indolent lymphomas are slow-growing forms of the disease, which can often be asymptomatic or have fewer symptoms upon diagnosis. Indolent lymphomas account for approximately 40% of all NHL cases. In patients with relapsed/refractory lymphoma, the disease has either responded to treatment but then returned or has not responded to initial treatment.

About AUGMENT
AUGMENT is a Phase 3, randomized, double-blind clinical trial evaluating the efficacy and safety of REVLIMID® (lenalidomide) in combination with rituximab (R²) versus rituximab plus placebo in patients with previously treated follicular lymphoma and marginal zone lymphoma. AUGMENT included patients diagnosed with Grade 1, 2 or 3a follicular lymphoma, who received at least 1 prior systemic therapy, were refractory or relapsed, not rituximab-refractory.

The primary endpoint was progression-free survival, defined as the time from date of randomization to the first observation of disease progression or death due to any cause. Secondary and exploratory endpoints included overall response rate, durable complete response rate, complete response rate, duration of response, duration of complete response, overall survival, event-free survival and time to next anti-lymphoma therapy.

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

REVLIMID is indicated as maintenance therapy in adult patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT)
REVLIMID is indicated for the treatment of adult 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 adult patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

REVLIMID in combination with a rituximab product is indicated for the treatment of adult patients with previously treated follicular lymphoma (FL).

REVLIMID in combination with a rituximab product is indicated for the treatment of adult patients with previously treated marginal zone lymphoma (MZL).

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

REVLIMID is only available through a restricted distribution program, REVLIMID REMS®.
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.

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe 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. Patients may require dose interruption and/or dose reduction. **MM:** Monitor complete blood counts (CBC) in patients taking REVLIMID + dexamethasone or REVLIMID as maintenance therapy, every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter. **MDS:** Monitor CBC in patients on therapy for del 5q MDS, weekly for the first 8 weeks of therapy and at least monthly thereafter. See Boxed WARNINGS for further information. **MCL:** Monitor CBC in patients taking REVLIMID for MCL weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. **FL/MZL:** Monitor CBC in patients taking REVLIMID for FL or MZL weekly for the first 3 weeks of Cycle 1 (28 days), every 2 weeks during Cycles 2-4, and then monthly 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 the 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 and in patients with FL or MZL receiving REVLIMID + rituximab therapy, an increase of hematologic plus solid tumor SPM, notably AML, have been observed. In MM patients, MDS was also observed. Monitor
patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment.

**Increased Mortality with Pembrolizumab:** In clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with MM with a PD-1- or PD-L1- blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID + dexamethasone. 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.

**Severe Cutaneous Reactions Including Hypersensitivity Reactions:** Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) 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, TEN, or DRESS is suspected and should not be resumed following discontinuation for these reactions.

**Tumor Lysis Syndrome (TLS):** Fatal instances of TLS have been reported during treatment with REVLIMID. The patients at risk of TLS are those with high tumor burden prior to treatment. Closely monitor patients at risk and take appropriate preventive approaches.

**Tumor Flare Reaction (TFR):** TFR has occurred during investigational use of REVLIMID for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL, FL, or MZL. 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 starting REVLIMID treatment and during therapy.

**Early Mortality in Patients With MCL:** In another MCL study, there was an increase in early deaths (within 20 weeks); 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥10 x 10^9/L).

**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%), pyrexia (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%)

**Follicular Lymphoma/Marginal Zone Lymphoma**

- Fatal adverse reactions occurred in 6 patients (1.5%) receiving REVLIMID + rituximab across both trials. Fatal adverse reactions (1 each) included: cardio-respiratory arrest, arrhythmia, cardiopulmonary...
failure, multiple organ dysfunction syndrome, sepsis, and acute kidney injury. The most frequent serious adverse reaction that occurred in the REVLIMID/rituximab arm was febrile neutropenia (3.0%).

- Grade 3 and 4 adverse reactions reported in ≥5% of patients treated in the FL/MZL trial with REVLIMID + rituximab were: neutropenia (50%) and leukopenia (7%)
- Adverse reactions reported in ≥15% of patients with FL/MZL treated with REVLIMID + rituximab were: neutropenia (58%), diarrhea (31%), constipation (26%), cough (24%), fatigue (22%), rash (22%), pyrexia (21%), leukopenia (20%), pruritus (20%), upper respiratory tract infections (18%), abdominal pain (18%), anemia (16%), headache (15%), thrombocytopenia (15%)

**DRUG INTERACTIONS**

Periodically monitor digoxin plasma levels 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 dexamethasone 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

- **Renal Impairment:** Adjust the starting dose of REVLIMID based on the creatinine clearance value and in patients on dialysis

Please see full **Prescribing Information**, including Boxed WARNINGS, for REVLIMID.

**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](http://www.celgene.com). Follow Celgene on Social Media: [@Celgene](https://twitter.com/Celgene), [Pinterest](https://www.pinterest.com/celgene/), [LinkedIn](https://www.linkedin.com/company/celgene-corporation), [Facebook](https://www.facebook.com/Celgene) and [YouTube](https://www.youtube.com/Celgene).

**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. Celgene undertakes 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 each company's 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 the Annual Report on Form 10-K and other reports of each company filed with the Securities and Exchange Commission, including factors related to the proposed transaction between Bristol-Myers Squibb and Celgene, such as, but not limited to, the risks that: management’s time and attention is diverted on transaction related issues; disruption from the transaction make it more difficult to maintain business, contractual and operational relationships; legal proceedings are instituted against Bristol-Myers Squibb, Celgene or the combined company could delay or prevent the proposed transaction; and Bristol-Myers Squibb, Celgene or the combined company is unable to retain key personnel.

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