CELGENE RECEIVES CHMP POSITIVE OPINION FOR REVLIMID® (LENALIDOMIDE) IN COMBINATION WITH RITUXIMAB FOR THE TREATMENT OF ADULT PATIENTS WITH PREVIOUSLY TREATED FOLLICULAR LYMPHOMA

REVLIMID® and rituximab (R²) has the potential to become a chemotherapy-free combination treatment option for patients with follicular lymphoma who have relapsed or did not respond to previous treatment.

The positive opinion was based on the results of the Phase 3 AUGMENT study, which showed the R² regimen conferred a statistically significantly improvement in progression-free survival versus rituximab monotherapy.

SUMMIT, NJ – Date – Celgene Corporation (NASDAQ: CELG) today announced that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending the approval of REVLIMID® (lenalidomide) in combination with rituximab (anti-CD20 antibody) (R²) for the treatment of adult patients with previously treated follicular lymphoma (FL) (Grade 1-3a). If approved by the European Commission (EC), R² will be the first combination treatment regimen for patients with FL that does not include chemotherapy.

“Since its initial approval in 2007, REVLIMID has continued to demonstrate its benefits across a range of serious blood disorders in Europe and a CHMP positive opinion for this combination with rituximab is very good news for patients with follicular lymphoma. We look forward to the European Commission decision,” said Tuomo Pätsi, President of Hematology/Oncology for Celgene Worldwide Markets.

In FL, a subtype of indolent NHL, the immune system is not functioning optimally.1,2 When this dysfunction occurs, the immune system either fails to detect or attack cancerous cells.1,2 Rituximab is a monoclonal antibody that targets the CD20 antigen on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab causes B-cell lysis. Lenalidomide is an immunomodulator that increases the number and activation of T and natural killer (NK) cells, resulting in the lysis of tumor cells. The R² combination regimen acts by complementary mechanisms to help the patient’s immune system to find and destroy the cancer cells.3

Given the incurable nature of FL,2 a high unmet medical need exists for the development of novel treatment options with new mechanisms of action and a tolerable safety profile to help improve progression-free survival (PFS) especially in the setting of previously treated FL.

The estimated incidence of NHL in Europe was 100,055 cases in 2018; FL accounts for approximately 25% of all NHL cases and is the most common form of indolent NHL.3,4,5

“Chemotherapy is a standard of care for indolent forms of NHL, but most patients will relapse or become refractory to their current treatment,” said Prof. John Gribben, President of EHA and Centre for Haemato-Oncology, Barts Cancer Institute, in England “The combination of REVLIMID and rituximab could represent a new, chemotherapy-free treatment option for patients with previously treated follicular lymphoma.”
The CHMP positive opinion is based primarily on results from the randomized, multi-center, 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). Additionally, findings from the MAGNIFY study were included as support for the safety and efficacy of lenalidomide plus rituximab in patients with relapsed or refractory FL, including rituximab refractory FL patients.

The CHMP reviews applications for all member states of the European Union (EU), as well as Norway, Liechtenstein, and Iceland. The European Commission, which generally follows the recommendation of the CHMP, is expected to make its final decision in approximately two months. If approval is granted, detailed conditions for the use of this product will be described in the REVLIMID Summary of Product Characteristics (SmPC), which will be published in the revised European Public Assessment Report (EPAR).

**About Follicular 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. Other differentiating factors of lymphomas are what type of lymphocyte is affected (T cell or B cell) and how mature the cells are when they become cancerous.

Follicular lymphoma is the most common indolent (slow-growing) form of NHL, accounting for approximately 25% of all Non-Hodgkin lymphoma (NHL) patients. Most patients present with advanced disease usually when lymphoma-related symptoms appear (e.g., nodal disease, B symptoms, cytopenia) and receive systemic chemoimmunotherapy. While follicular lymphoma patients are generally responsive to initial treatment, the disease course is characterized by recurrent relapses over time with shorter remission periods.

**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 (FL). AUGMENT included patients diagnosed with Grade 1, 2 or 3a FL, who were previously treated with at least 1 prior systemic therapy and two previous doses of rituximab. Patients were documented relapsed, refractory or progressive disease following systemic therapy, but were 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 is approved in Europe and the United States as monotherapy, indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who have undergone autologous stem cell transplantation. REVLIMID as combination therapy is approved in Europe, in the United States, in Japan and in around 25 other countries for the treatment of adult patients with previously untreated MM who are not eligible for transplant. REVLIMID is also approved in combination with dexamethasone for the treatment of patients with MM who have received at least one prior therapy in nearly 70 countries, encompassing Europe, the Americas, the Middle-East and Asia, and in combination
with dexamethasone for the treatment of patients whose disease has progressed after one therapy in Australia and New Zealand.

REVLIMID is also approved in the United States, Canada, Switzerland, Australia, New Zealand and several Latin American countries, as well as Malaysia and Israel, for transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and in Europe for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

In addition, REVLIMID is approved in Europe for the treatment of patients with mantle cell lymphoma (MCL) and in the United States for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. In Switzerland, REVLIMID is indicated for the treatment of patients with relapsed or refractory MCL after prior therapy that included bortezomib and chemotherapy/rituximab.

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
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. **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. **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.

Increased Mortality with Pembrolizumab: In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma 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/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.

Severe Cutaneous Reactions: 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. Consider REVLIMID interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue REVLIMID for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN, or DRESS.

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.

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 10⁹/L).

Hypersensitivity: Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to REVLIMID has been reported. Permanently discontinue REVLIMID for angioedema and anaphylaxis.

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 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 $C_{\text{max}}$ 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 in patients on dialysis

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

Please see full SmPC for further information.

**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), [Pinterest](https), [LinkedIn](https), [Facebook](https) and [YouTube](https).
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.

For enquiries, please contact:

Celgene Corporation
Investors:
Nina Goworek
+1-908-673-9711 ngoworek@celgene.com
or
Media:
+1-908-673-2275 media@celgene.com
