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Oral Anti-Cancer Therapy REVLIMID® Receives Positive CHMP Opinion as Treatment for Patients with Form of Rare Blood Cancer Deletion 5Q Myelodysplastic Syndromes

BOUDRY, Switzerland--(BUSINESS WIRE)--Apr. 26, 2013-- Celgene International Sàrl (NASDAQ: CELG) today announced the European Medicines Agency's (EMA): Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for REVLIMID® for the treatment of patients with transfusion-dependent anemia due to low or intermediate-1-risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

The CHMP, which reviews applications for all 27 member states in the European Union (EU), as well as Norway and Iceland, has recommended approval for REVLIMID in this indication. The European Commission, which generally follows the recommendation of the CHMP, is expected to make its final decision within two to three months. If approval is granted, detailed conditions for the use of this product will be described in the updated summary of product characteristics (SmPC), which will be published in the revised European public assessment report (EPAR).

MDS is a type of cancer where the production of blood cells and platelets by the bone marrow is disrupted, which can often lead to severe anemia, infections and bleeding. Approximately 50 percent of individuals with MDS will have some form of chromosome (cytogenetic) abnormality, and 30 percent of those are likely to have the specific del(5q) abnormality. In general, MDS del(5q) is associated with a poor prognosis – especially when other cytogenetic abnormalities are present – as well as an increased risk of MDS progressing to acute myeloid leukemia (AML).

"The CHMP's positive opinion is an important milestone in Celgene's effort to bring REVLIMID to patients with MDS throughout the EU who have an isolated del(5q) cytogenic abnormality," said Alan Colowick, President of Celgene EMEA. "Following the final decision by the European Commission within the next few months, we can begin the work of partnering with our many stakeholders to ensure patients have access to this new treatment option."

The CHMP positive opinion was based on the results of MDS-004, a phase III, multi-center, randomized, double-blind, placebo-controlled clinical study. The largest trial of MDS del(5q) patients conducted to-date, MDS-004 compared the efficacy and safety of once-daily oral treatment with REVLIMID (5 or 10 mg orally once daily on days 1-21 of repeated 28-day cycles) to placebo in 205 patients at 37 participating centers throughout Europe.

About REVLIMID

REVLIMID is approved in combination with dexamethasone for the treatment of patients with multiple myeloma 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 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 MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Marketing Authorization Applications are currently being evaluated in a number of other countries.

U.S. Regulatory Information for Revlimid

REVLIMID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.

REVLIMID® (lenalidomide) 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.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS 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 (formerly known as the "RevAssist®"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 THROMBOEMBOLISM

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with MM who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

CONTRAINDICATIONS

Pregnancy:

- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

Allergic Reactions:

- 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:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks

following discontinuation of REVLIMID therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- 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 28 days 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 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

REVLIMID REMS Program

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) the **REVLIMID REMS** Program (**formerly known as the "RevAssist®" Program**). Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements. . Further information about the **REVLIMID REMS** program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436

Hematologic Toxicity—Multiple Myeloma: REVLIMID can cause significant neutropenia and thrombocytopenia**.** Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. In the pooled MM studies Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone. Patients may require dose interruption and/or dose reduction

Venous Thromboembolism: Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MM treated with lenalidomide combination therapy and patients with MDS treated with lenalidomide monotherapy

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 REVLIMID treatment should be evaluated in patients with lactose intolerance

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

Tumor Flare Reaction: Tumor flare reaction has occurred during investigational use of lenalidomide for chronic lymphocytic leukemia (CLL) and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Treatment of CLL or lymphoma with lenalidomide outside of a well-monitored clinical trial is discouraged

Hepatotoxicity: Cases of transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with lenalidomide. Treatment with lenalidomide should be interrupted until the levels return to baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients

Second Primary Malignancies: Patients with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide

ADVERSE REACTIONS

Multiple Myeloma

- In the REVLIMID/dexamethasone treatment group, 269 patients (76%) underwent at least one dose interruption with or without a dose reduction of REVLIMID compared to 199 patients (57%) in the placebo/dexamethasone treatment group
- Of these patients who had one dose interruption with or without a dose reduction, 76% (269/353) vs 57% (199/350), 50% in the REVLIMID/dexamethasone treatment group underwent at least one additional dose interruption with or without a dose reduction compared to 21% in the placebo/dexamethasone treatment group
- Most adverse events and Grade 3/4 adverse events were more frequent in MM patients who received the combination of REVLIMID/dexamethasone compared to placebo/dexamethasone

- Grade 3/4 neutropenia occurred in 33.4% vs 3.4%; 2.3% experienced Grade 3/4 febrile neutropenia vs 0% in the REVLIMID/Dexamethasone vs. the placebo/Dexamethasone treatment groups respectively
- Deep vein thrombosis (DVT) was reported as a serious adverse drug reaction (7.4%) or Grade 3/4 (8.2%) in the REVLIMID/Dexamethasone treatment group compared to 3.1% and 3.4% in the placebo/Dexamethasone treatment group. Discontinuations due to DVT were reported at comparable rates between groups
- Pulmonary embolism (PE) was reported as a serious adverse drug reaction (3.7%) or Grade 3/4 (4.0%) in the REVLIMID/Dexamethasone treatment group compared to 0.9% and 0.9% in the placebo/Dexamethasone treatment group. Discontinuations due to PE were reported at comparable rates between groups
- Adverse reactions reported in ≥15% of MM patients (REVLIMID/dexamethasone vs dexamethasone/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%), weight decreased (20% vs 15%), nasopharyngitis (18% vs 9%), blurred vision (17% vs 11%), anorexia (16% vs 10%), and dysgeusia (15% vs 10%)

Myelodysplastic Syndromes

- Thrombocytopenia (61.5%; 91/148) and neutropenia (58.8%; 87/148) were the most frequently reported adverse events observed in the del 5q MDS population
- 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%)
- Other adverse events reported in ≥15% of del 5q MDS patients (REVLIMID): 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%)

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin. Erythropoietic agents, or other agents, that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436

Nursing Mothers: It is not known whether REVLIMID is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother

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

Geriatric Use: Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function

Renal Impairment: Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS

About Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a group of hematologic malignancies that affect approximately 300,000 people worldwide. Myelodysplastic syndromes occur when blood cells remain in an immature or “blast” stage within the bone marrow and never develop into mature cells capable of performing their necessary functions. Eventually, the bone marrow may be filled with blast cells suppressing normal cell development. MDS patients must often rely on blood transfusions to manage symptoms

of anemia and fatigue and may develop life-threatening iron overload and/or toxicity from frequent transfusions, thus underscoring the critical need for new therapies targeting the cause of the condition rather than simply managing its symptoms.

About Deletion 5q Chromosomal Abnormality

Chromosomal (cytogenetic) abnormalities are detected in more than half of patients with myelodysplastic syndrome (MDS), and involve a deletion in all or part of one or more specific chromosomes. The most common cytogenetic abnormalities in MDS are deletions in the long arm of chromosomes 5, 7, and 20. Another common abnormality is an extra copy of chromosome 8. A deletion involving the 5q chromosome may be involved in 20 percent to 30 percent of all MDS patients.

About Celgene International Sárl

Celgene International Sárl, located in Boudry, Switzerland, is a wholly owned subsidiary and international headquarters of Celgene Corporation. Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through gene and protein regulation. For more information, please visit the Company's website at www.celgene.com.

Celgene has been operating in Europe since 2006 and is currently present in 22 EU countries. By utilizing the latest advances in molecular and cellular research to develop novel therapies that target the mechanisms of disease at their source, Celgene is driving clinical advances in debilitating diseases for patients with the biggest unmet medical needs.

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