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REVLIMID® (Lenalidomide) Approved by the European Commission as Monotherapy for the Maintenance Treatment of Patients with Newly Diagnosed Multiple Myeloma after Autologous Stem Cell Transplantation

- **Oral REVLIMID® is the first and only medicine licensed in Europe for use as post-autologous stem cell transplantation maintenance therapy in multiple myeloma**
- **The new indication expands the availability of REVLIMID® across the disease continuum of multiple myeloma**

BOUDRY, Switzerland--(BUSINESS WIRE)-- Celgene International Sàrl, a wholly-owned subsidiary of Celgene Corporation (NASDAQ: CELG), today announced that the European Commission (EC) has approved REVLIMID® (lenalidomide) as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (ASCT). REVLIMID® is the first and only licensed maintenance treatment available to these patients.

The REVLIMID® Marketing Authorisation has been updated to include this new indication, which expands on the existing multiple myeloma indications as combination therapy for the treatment of those not eligible for transplant who are newly diagnosed, or have received at least one prior therapy.

Multiple myeloma is an incurable and life-threatening blood cancer that is characterised by tumour proliferation and suppression of the immune system.[1] It is a rare but deadly disease: around 39,000 people are diagnosed with multiple myeloma in Europe, and around 24,000 people die from the disease each year.[2] The median age at diagnosis in Europe is between 65 and 70 years.[3] In Europe, patients who are fit and in good clinical condition are typically considered eligible for ASCT.[4]

For patients who are newly diagnosed with multiple myeloma and eligible for ASCT, key treatment goals are to delay disease progression and ultimately achieve long-term control over multiple myeloma.[5] These patients typically receive induction therapy and high-dose chemotherapy with melphalan followed by ASCT. This treatment approach has been an established standard of care for over 20 years.[6] Considering that over half of those patients who relapse do so within 2 to 3 years of ASCT,[7,8] the approval of a maintenance therapy for use after ASCT that may delay disease progression represents a major advance for these patients.

"After ASCT, most patients will still see their disease recur or progress. We now have an opportunity to enhance immune function and delay disease progression by controlling residual malignant cells and slowing tumour growth. REVLIMID® has been shown to increase progression-free survival after ASCT in clinical trials. Having a licensed therapy for use in this very important setting means we now have the opportunity to delay disease progression by sustaining the response," says Professor Michel Attal, Executive Director of the *Institut Universitaire du Cancer Toulouse Oncopole and Institut Claudius Regaud*, France.

The EC decision to approve REVLIMID® as monotherapy for multiple myeloma in the post-ASCT setting was based on the results of two cooperative group-led studies, CALGB 100104[9] and IFM 2005-02.[10]

- CALGB 100104 was a phase III, controlled, double-blind, multi-centre study of 460 patients with newly diagnosed multiple myeloma undergoing ASCT who were randomized to receive continuous daily treatment with REVLIMID® or placebo until relapse or intolerance.
- IFM 2005-02 was an international, phase III, controlled, double-blind, multi-centre study of 614 patients newly

diagnosed with multiple myeloma who were randomized to receive a 2-month consolidation regimen post-ASCT of REVLIMID® monotherapy, followed by continuous daily treatment with either REVLIMID® or placebo until relapse or intolerance.

In both studies, the primary efficacy endpoint in the study was progression-free survival (PFS) from transplant to the date of disease progression or death, whichever occurred first. REVLIMID® monotherapy as maintenance treatment post-ASCT significantly reduced the risk of disease progression or death in patients with multiple myeloma, leading to the studies being unblinded based on passing their pre-specified boundary for superiority at interim analysis. The updated PFS, using a cut-off of 1 February 2016 continues to show a PFS advantage:

- CALGB 100104: after 81.6 months of follow up, median PFS was 56.9 months (95% CI 41.9, 71.7) in the REVLIMID® arm versus 29.4 months (95% CI 20.7, 35.5) in the placebo arm (HR=0.61; 95% CI 0.48, 0.76; p < 0.001).
- IFM 2005-02: after 96.7 months of follow up, median PFS was 44.4 months (95% CI 39.6, 52.0) in the REVLIMID® arm versus 23.8 months (95% CI 21.2, 27.3) in the placebo arm (HR=0.57; 95% CI 0.47, 0.68; p < 0.001).

Individual studies were not powered for an overall survival (OS) endpoint. Using a cut-off of 1 February 2016, a descriptive analysis showed that the median overall survival in the CALGB 100104 was 111.0 months (95% CI, 101.8, not estimable) for patients who received REVLIMID versus 84.2 (95% CI 71.0, 102.7) in the placebo arm (HR=0.61; 95% CI 0.46, 0.81; p < 0.001). In the IFM 2005-02 study, median overall survival was 105.9 months (95% CI, 88.8, not estimable) for patients who received REVLIMID versus 88.1 (95% CI 80.7, 108.4) in the placebo arm (HR=0.90; 95% CI 0.72, 1.13; p=0.355, not significant).

In both of these phase III studies, the safety profile was in line with other clinical data in newly diagnosed non-stem cell transplant and a post-approval safety study in relapsed/refractory multiple myeloma. The most commonly reported adverse events in these two studies were haematological, and included neutropenia and thrombocytopenia. The most commonly reported non-haematological adverse events were infections. An increased incidence rate of haematological second primary malignancies (SPMs) was also observed in the REVLIMID® group compared with the placebo group in both studies. However, the EC decision confirms that the benefit-risk ratio for REVLIMID® is positive in this expanded indication.

Tuomo Pätsi, President of Celgene European and International Operations, said, *"We are glad to provide a treatment option for these patients with multiple myeloma, who have previously had no licensed medicine available to them for maintenance treatment following ASCT. This latest approval underlines the important role of REVLIMID® in the treatment of multiple myeloma, extending its use across the disease spectrum, and demonstrating our commitment to multiple myeloma patients. We continue to invest in research and development as we strive to turn multiple myeloma - and other currently incurable diseases - into manageable conditions."*

The EC decision for the use of REVLIMID® as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone ASCT follows the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) in January 2017.

Celgene announced on 22 February 2017 that the U.S. Food and Drug Administration (FDA) has expanded the existing indication for REVLIMID® to include use for patients with multiple myeloma as maintenance therapy following autologous hematopoietic stem cell transplant in the U.S.

About CALGB 100104

CALGB 100104 was a phase III, randomised, controlled, double-blind, multi-centre study conducted in 47 centres in the United States. A total of 460 patients newly diagnosed with multiple myeloma - aged between 18 and 70 years - who achieved at least stable disease or better 100 days after undergoing autologous stem cell transplant, were randomised to receive either REVLIMID® maintenance (10 mg/day for 3 months, then 15 mg/day) or placebo, until disease progression, intolerable side effects or death.

About IFM 2005-02

IFM 2005-02 was a phase III, controlled, double-blind, multi-centre study conducted in 77 centres across 3 countries in Europe. A total of 614 patients newly diagnosed with multiple myeloma, who were younger than 65 years without signs of disease progression within 6 months of undergoing autologous stem cell transplant, were then randomised to receive a 2-month consolidation regimen of REVLIMID® monotherapy, 25 mg per day on 21/28 days, followed by either REVLIMID® maintenance (10 mg/day for 3 months, then 15 mg/day) or placebo, until disease progression, intolerable side effects or

death.

About REVLIMID®

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 multiple myeloma (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 and in the United States 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. 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.

ADDITIONAL IMPORTANT SAFETY INFORMATION based on EU SmPC

Contraindications

REVLIMID® (lenalidomide) is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients in the formulation.

REVLIMID® (lenalidomide) is contraindicated during pregnancy, and also in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Warnings and precautions

Pregnancy: the conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Cardiovascular disorders: patients with known risk factors for myocardial infarction or thromboembolism should be closely monitored.

Neutropenia and thrombocytopenia: complete blood cell counts should be performed every week for the first 8 weeks of treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required.

Infection with or without neutropenia: all patients should be advised to seek medical attention promptly at the first sign of infection.

Renal impairment: monitoring of renal function is advised in patients with renal impairment.

Thyroid disorders: optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Tumour lysis syndrome: patients with high tumour burden prior to treatment should be monitored closely and appropriate precautions taken.

Allergic reactions: patients who had previous allergic reactions while treated with thalidomide should be monitored closely.

Severe skin reactions: REVLIMID® (lenalidomide) must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance: patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Second primary malignancies (SPM): the risk of occurrence of hematologic SPM must be taken into account before initiating treatment with REVLIMID® (lenalidomide) either in combination with melphalan or immediately following high-dose melphalan and autologous stem cell transplant (ASCT). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Hepatic disorders: dose adjustments should be made in patients with renal impairment. Monitoring of liver function is recommended, particularly when there is a history of or concurrent viral liver infection or when REVLIMID® (lenalidomide) is combined with medicinal products known to be associated with liver dysfunction.

Newly diagnosed multiple myeloma patients: patients should be carefully assessed for their ability to tolerate REVLIMID® (lenalidomide) in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr < 60 mL/min.

Cataract: regular monitoring of visual ability is recommended.

Summary of the safety profile in multiple myeloma

Newly diagnosed multiple myeloma: patients who have undergone ASCT treated with REVLIMID® (lenalidomide) maintenance:

- The serious adverse reactions observed more frequently (≥5%) with REVLIMID® (lenalidomide) maintenance than placebo were pneumonias (10.6%) and lung infection (9.4%)
- The adverse reactions observed more frequently with REVLIMID® (lenalidomide) maintenance than placebo were neutropenia (79.0%), thrombocytopenia (72.3%), diarrhoea (54.5%), bronchitis (47.4%), nasopharyngitis (34.8%), muscle spasms (33.4%), leucopenia (31.7%), rash (31.7%), asthenia (29.7%), cough (27.3%), upper respiratory tract infection (26.8%), fatigue (22.8%), gastroenteritis (22.5%), anaemia (21.0%), and pyrexia (20.5%).

Newly diagnosed multiple myeloma: patients who are not eligible for transplant treated with REVLIMID® (lenalidomide) in combination with low dose dexamethasone:

- The serious adverse reactions observed more frequently (≥5%) with REVLIMID® (lenalidomide) in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were pneumonia (9.8%) and renal failure (including acute) (6.3%).
- The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma: patients who are not eligible for ASCT treated with REVLIMID® (lenalidomide) in combination with melphalan and prednisone:

- The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and REVLIMID® (lenalidomide) followed by REVLIMID® (lenalidomide) maintenance (MPR+R) or melphalan prednisone, and REVLIMID® (lenalidomide) followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were febrile neutropenia (6.0%) and anaemia (5.3%).
- The adverse reactions observed more frequently with MPR+R or MPR+p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Patients with multiple myeloma who have received at least one prior therapy:

- The most serious adverse reactions observed more frequently with REVLIMID® (lenalidomide) and dexamethasone than with placebo and dexamethasone in combination were venous thromboembolism (deep vein thrombosis, pulmonary embolism) and grade 4 neutropenia.
- The observed adverse reactions which occurred more frequently with REVLIMID® (lenalidomide) and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Special populations

Paediatric population: REVLIMID® (lenalidomide) should not be used in children and adolescents from birth to less than 18 years.

Older people with newly diagnosed multiple myeloma: for patients older than 75 years of age treated with REVLIMID® (lenalidomide) in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years who are treated with REVLIMID® (lenalidomide) in combination with melphalan and prednisone.

Older people with multiple myeloma who have received at least one prior therapy: care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment: care should be taken in dose selection and monitoring of renal function is advised. No dose adjustments are required for patients with mild renal impairment and multiple myeloma. Dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.

Patients with hepatic impairment: REVLIMID® (lenalidomide) has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Please refer to the Summary of Product Characteristics for full European prescribing information.

ABOUT CELGENE

Celgene International Sàrl, 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 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. 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 Celgene'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 Celgene's Annual Report on Form 10-K and other reports filed with the Securities and Exchange Commission.

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[9] McCarthy PL, et al. *N Engl J Med*. 2012;366(19):1770-1781. CALGB is the cooperative group Cancer and Leukemia Group B (now known as Alliance).

[10] Attal M, et al. *N Engl J Med*. 2012;366(19):1782-1791. IFM is the cooperative group Intergroupe Francophone du Myélome.

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