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# Celgene Receives Positive CHMP Opinion to Expand REVLIMID® (Lenalidomide) Indication as Monotherapy for the Maintenance Treatment of Patients with Newly Diagnosed Multiple Myeloma (MM) after Autologous Stem Cell Transplantation

- **REVLIMID® is the first and only medicine granted positive CHMP opinion for post-Autologous Stem Cell Transplantation (ASCT) maintenance therapy in MM**
- **The new indication expands the availability of REVLIMID® across the disease continuum of MM**

BOUDRY, Switzerland--(BUSINESS WIRE)-- **Celgene International Sàrl,** a wholly owned subsidiary of 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 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 (ASCT). Once approved by the European Commission, REVLIMID® will be the first and only licensed maintenance treatment available to these patients.

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 MM 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 under 65 years, fit and in good clinical condition are typically considered eligible for ASCT.[4]

For newly diagnosed, transplant-eligible MM patients, key treatment goals are to obtain and to maintain a deep response to therapy, with the ultimate objective of delaying disease progression.[5,6] 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.[7] Considering that over half of patients relapse within 2 to 3 years after ASCT,[8,9] trials have been conducted to assess whether maintenance therapy following ASCT could enable more durable remissions.

*"Studies show that maintenance treatment after ASCT with REVLIMID® may help control residual malignant cells and delay tumour growth by enhancing immune function,"* says Professor Michel Attal, Executive Director of the *Institut Universitaire du Cancer Toulouse Oncopole and Institut Claudius Regaud*, France*. "Our primary goal is to delay disease progression for as long as possible, and we have seen in several independent studies, that REVLIMID® maintenance after ASCT can halve the risk of disease progression by sustaining the response."*

The CHMP recommendation was based on the results of two cooperative group-led studies, CALGB 100104[10] and IFM 2005-02[11]:

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

In the two phase III studies, REVLIMID® monotherapy as maintenance treatment post-ASCT significantly reduced the risk of disease progression or death in patients with MM, leading to the studies being unblinded based on passing their pre-specified boundary for superiority at interim analysis.

In these studies, the safety profile was in line with other clinical data in newly diagnosed non-stem cell transplant (NSCT) and post-approval safety study in relapsed/refractory MM (rrMM). Across both phase III clinical studies, the most commonly reported adverse events (AE) were haematological and included neutropenia and thrombocytopenia. The most commonly reported non-haematological AE were infections. In both trials, an increased incidence rate of haematologic second primary malignancies (SPMs) has been observed in the REVLIMID® group compared with the placebo group. However, the CHMP positive opinion confirms that the benefit-risk ratio for REVLIMID® is positive in this expanded indication.

Tuomo Pätsi, President of Celgene in Europe, the Middle East and Africa (EMEA), said, *"Despite substantial progress made so far in multiple myeloma treatment, it remains an incurable disease. We welcome this CHMP opinion as it confirms the important role that REVLIMID® plays in treating multiple myeloma, extending the use of REVLIMID® across the disease continuum. At Celgene, we aspire to turn some of the most challenging diseases, like multiple myeloma, into manageable conditions. Therefore, we will continue to invest more than one-third of our revenues back into research and development."*

The CHMP reviews applications for all 28 member states in 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 Summary of Product Characteristics (SmPC), which will be published in the revised European Public Assessment Report (EPAR).

**About CALGB 100104**

CALGB 100104 was a phase III, randomised, controlled, double-blind, multi-centre study conducted in 47 centres in the United States. 460 newly diagnosed multiple myeloma patients - aged between 18 and 70 years - who achieved at least stable disease (SD) or better 100 days after undergoing autologous stem cell transplant (ASCT), 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. 614 newly diagnosed multiple myeloma patients younger than 65 years without signs of disease progression within 6 months of undergoing ASCT, were then randomised to receive a two-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® in combination with dexamethasone 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.

**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 in patients 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 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 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 Celgene's Annual Report on Form 10-K and other reports filed with the Securities and Exchange Commission.*



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[1] Palumbo A, et al. *N Engl J Med*. 2011;364:1046-1060.

[2] Ferlay J, et al. *Eur J Cancer*. 2013;49:1374-1403

[3] Moreau P, et al. *Ann Oncol*. 2013; 24 (Suppl 6): vi133-vi137

[4] Moreau P, et al. *Ann Oncol*. 2013; 24 (Suppl 6): vi133-vi137

[5] Stewart AK, et al. *Blood*. 2009;114:5436-5443.

[6] Hoering A, et al. *Blood*. 2009;114:1299-1305

[7] Bird JM, et al. *Br J Haematol*. 2011;154:32-75

[8] Attal M, et al. *Blood*. 2006 Nov 15;108(10):3289-94

[9] Child JA, et al. *N Engl J Med.* 2003; 348:1875-1883

[10] 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).

[11] 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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