*08 April 2013*

**Direct Healthcare Professional Communication on the risk of haematologic second primary malignancies in patients treated with thalidomide**

Dear Healthcare Professional:

Celgene Europe Limited would like to inform you of the following:

**Summary**

- A statistically significant increase in the risk of haematologic second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes (AML/MDS)) has been observed in an ongoing study in patients with previously untreated multiple myeloma receiving melphalan, prednisone, and thalidomide, compared with patients treated with lenalidomide plus dexamethasone.
- The risk of haematologic second primary malignancies with thalidomide increased over time, to approximately 2% after 2 years and 4% after 3 years.
- Before starting thalidomide treatment in combination with melphalan and prednisone, take into account both the benefit achieved with thalidomide and the risk of acute myeloid leukaemia and myelodysplastic syndromes.
- Carefully evaluate patients before and during treatment using standard cancer screening and provide appropriate treatment.

This information is being sent in agreement with the Irish Medicines Board (IMB) and the European Medicines Agency.

**Further information on the safety concern and the recommendations**

Thalidomide (Celgene) is licensed in the European Union for use in combination with melphalan and prednisone as first-line treatment of patients with untreated multiple myeloma who are aged ≥65 years or ineligible for high-dose chemotherapy.

A detailed review of the ongoing MM-020 clinical study was prompted by the observation of an imbalance in haematologic SPMs.

The study review showed that a higher percentage of patients who received melphalan, prednisone, and thalidomide were diagnosed with AML/MDS (1.8%) than those treated with lenalidomide plus dexamethasone (0.3%). The risk with thalidomide increased over time to approximately 2% after 2 years and 4% after three years. The median observation time in this ongoing clinical study is 22.3 months.

The observed cases signal an increased risk of AML/MDS with thalidomide when combined with melphalan, a known leukaemogenic agent, in newly diagnosed multiple myeloma patients. Cross-study comparisons between study MM-020(1) and study MM-015(2) indicate that the relative risk for developing AML/MDS is three times higher for patients receiving melphalan, prednisone, and thalidomide, compared with patients receiving melphalan and prednisone alone (hazard ratio=0.31, 95% CI: 0.07, 1.47).

An increased risk of second primary malignancies, including acute myeloid leukaemia and myelodysplastic syndromes, has also been observed in patients with newly diagnosed multiple myeloma receiving lenalidomide in combination with melphalan, or immediately following high-dose melphalan and autologous stem cell transplantation.

Product information for thalidomide (Celgene) has been updated to reflect this risk (see Annex).

Adverse reactions associated with the use of Thalidomide Celgene should be reported in accordance with the national spontaneous reporting system.

Please report suspected adverse reactions with any medicine to the Irish Medicines Board using the on-line reporting function on the IMB website (www.imb.ie) or alternatively by contacting the IMB on +353-1-676 4971.

Adverse reactions associated with the use of Thalidomide Celgene may also be reported to Celgene. Please contact Celgene Drug Safety as below:

Celgene Drug Safety
Celgene Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB

Telephone: 1800 936 217
Fax: 1800 936 477
Email: drugsafetyuk@celgene.com

**Further information**

If you have any further questions or require further information, please contact Celgene Medical Information as below:

Telephone: 1800 333 111
Fax: 1800 333 112
E-mail: medinfo.uk.ire@celgene.com

This communication has been addressed to you as the Supervising Pharmacist of a Pharmacy registered to dispense Thalidomide Celgene. Although this has also been sent to Haematologists and potential prescribers of Thalidomide, we would appreciate that if this could be brought to the attention of any of any other Thalidomide dispensers or prescribers in your hospital, clinic or pharmacy.

Yours faithfully,

Dr David P. Gillen
Medical Director, UK and Ireland
Celgene Limited

**Annexes:**

Tracked-change copy of the Thalidomide (Celgene) Summary of Product Characteristics and Patient Information Leaflet.

**References:**

[1] Study MM-020 – Phase 3, multicenter, randomized, open-label, 3-arm study to determine the efficacy and safety of lenalidomide plus low-dose dexamethasone when given until progressive disease or for 18 four-week cycles versus the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles in newly diagnosed MM subjects either ≥ 65 years or not candidates for stem cell transplant

[2] Study MM-015 – Phase 3 multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel-group study to determine the efficacy and safety of lenalidomide (R; 10 mg daily dose) in combination with standard-dose melphalan/prednisone (MP) versus placebo plus melphalan and prednisone (MPp) in subjects with newly diagnosed MM who are 65 years of age or older and ineligible for autologous stem cell transplant.