10 December 2012

Direct Healthcare Professional Communication on the risk of hepatic disorders associated with Revlimid® (lenalidomide) use, in the context of other risk factors.

Dear Healthcare Provider:

Celgene, in agreement with the European Medicines Agency and the Irish Medicines Board wishes to inform you about important safety information following a recent review of Revlimid® (lenalidomide).

Summary

- In multiple myeloma patients treated with lenalidomide in combination with dexamethasone, some severe cases of liver injuries, including fatal cases, have been reported: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis and mixed cytolytic/cholestatic hepatitis.
- Lenalidomide is excreted by the kidneys. It is important to adjust the dose of lenalidomide in patients with renal impairment to avoid high plasma levels which may increase the risk of more severe haematological side effects or hepatotoxicity.
- The mechanisms of severe drug-induced hepatotoxicity remain unknown and risk factors might be pre-existing viral liver disease, elevated baseline liver-enzymes, and possibly treatment with antibiotics.
- Monitoring of liver function is recommended, particularly when there is a history of, or concurrent, viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction such as paracetamol.

Additional information on hepatic disorder events

A safety review of hepatic disorders in the Celgene Pharmacovigilance database as of 26 December 2011, noted an overall reporting rate of 0.67% for hepatic disorders in the patient population exposed to lenalidomide. These reports were mostly of liver-related investigations, signs and symptoms. The reporting rate of hepatic failure, fibrosis and cirrhosis, cholestasis and jaundice as well as non-infectious hepatitis was low. There were a few cases with a fatal outcome and most were complicated by advanced malignant disease, previous or active liver disease, and multiple co-morbidities. The mechanisms involved in the physiopathology remain unknown but a causal relationship between lenalidomide and hepatic disorders cannot be excluded

Co-morbid conditions and other risk factors that may have contributed to the hepatic disorders include a history of hepatic and renal disorders or concurrent liver infection, or concomitant medications known to cause severe liver dysfunction such as paracetamol.

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The revised summary of product characteristics has been agreed with the EU Competent Authorities**.**

Call for reporting

Adverse reactions associated with the use of Revlimid 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 fhte IMB website (www.imb.ie) or alternatively by contacting the IMB on +353-1-676 4971.

Adverse reactions associated with the use of Revlimid 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

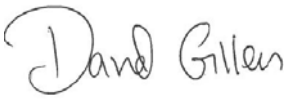
Telephone: 1800 936 217
Fax: 1800 936 477
Email: drugsafetyuk@celgene.com

Communication 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

Yours faithfully,



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

Annexes:
Tracked-change copy of the Revlimid® (lenalidomide) Summary of Product Characteristics