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6th November 2012

ML158

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 Medicines Authority, 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**.**

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Call for reporting

Please be reminded that adverse reactions associated with the use of Revlimid should be reported in accordance with the national spontaneous reporting system as follows:

Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: http://www.medicinesauthority.gov.mt/pub/adr.doc

Communication information

If you have any further questions or require further information, please contact your local Celgene representative at AM Mangion Ltd.

AM Mangion Limited Pharmacovigilance Contact Services:
24 hr Tel No. : 23976333
Fax : 23976123
email : pv@ammangion.com.mt

Annexes:

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

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PHARMACOVIGILANCE COMMUNICATION PLAN

PRODUCT: Revlimid (lenalidomide)
MARKETING AUTHORISATION HOLDER: Celgene Europe Limited
PROCEDURE NUMBER: EMEA/H/C/00717/II/0058
SAFETY CONCERN: Potential risk of hepatic disorders
COMUNICATION OBJECTIVE: Information on the association of Revlimid (lenalidomide) in combination with other risk factors on the potential risk of hepatic disorders in multiple myeloma.
LIST OF COMMUNICATION DOCUMENTS: Direct Healthcare Professional Communication

COMMUNICATION DOCUMENT Direct Healthcare Professional Communication Target population: Healthcare professionals who may prescribe (physicians) or dispense (pharmacists) lenalidomide - details to be confirmed, upon discussions with national competent authorities (NCAs) Dissemination mechanism: Details to be agreed with national competent authorities Other recipients: Details on distribution list to be agreed with national competent authorities
STRATEGY FOR POST-COMMUNICATION PHASE: Update of relevant DHPC sections of the Educational kit if appropriate for the Member State concerned and distribution to healthcare professionals

TIMETABLE for DHPC:	
Anticipated date of agreement by CHMP on DHPC and Communication Plan	Date of CHMP opinion
Target time for translations from MAH to NCA	Day of Commission Decision
Confirmation of Translation by NCA to MAH	In accordance to national timelines and in agreement with NCAs

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TIMETABLE for DHPC:	
Date and time of release of information to the public in the EU	Within 2-4 weeks upon receipt of Commission Decision and in accordance to NCA timelines and discussions