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Direct Healthcare Professional Communication

20th June 2017

Ibrutinib (IMBRUVICA®) and risk of hepatitis B reactivation: Hepatitis B virus status to be established before initiating treatment with IMBRUVICA

Dear Healthcare Professional,

Janssen-Cilag International N.V. in agreement with the European Medicines Agency (EMA) and the Malta Medicines Authority would like to inform you of the following:

Summary

Cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving ibrutinib (IMBRUVICA), therefore:

- **Patients should be tested for HBV infection before starting treatment with IMBRUVICA.**
- **If patients have positive hepatitis B serology, consultation with a liver disease expert is recommended before starting treatment with IMBRUVICA.**
- **Patients with positive hepatitis B serology who require Imbruvica should be monitored and managed according to local medical standards of care to prevent hepatitis B virus (HBV) reactivation.**

Background on the safety concern and recommendations

A cumulative review of data from clinical trials and postmarketing cases has identified reports of hepatitis B reactivation in ibrutinib-treated patients. To date, there have been no reports of fulminant liver failure leading to liver transplantation. However, one fatal case has been reported which was due to hepatitis B reactivation and concurrent metastatic melanoma of the liver, lung and spleen. The time-to-onset of hepatitis B reactivation was variable with no clear pattern. Ibrutinib was discontinued or interrupted in the majority of cases. In general patients were managed with HBV antiviral medication according to their local standard of care and as a result there was a reduction in HBV viral load. In some cases, the role of ibrutinib therapy in the onset of the event was confounded by prior or concomitant chemoimmunotherapy associated with viral reactivation. Some of the patients had a documented history of hepatitis B and in other cases baseline hepatitis B serology status was not reported.

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Among patients in company sponsored clinical trials, the frequency of hepatitis B reactivation is uncommon (0.2%). Patients with active hepatitis B were excluded from these sponsored trials.

The Summary of Product Characteristics (SmPC) and the package leaflet for IMBRUVICA will be updated to reflect the new safety information, as recommended by the European Medicines Agency (EMA) and National Competent Authorities.

Call for reporting

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC on how to report adverse reactions.

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with this product in accordance with the national spontaneous reporting system. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

Alternatively kindly contact directly Mr Claude Vella Bonanno at A.M. Mangion Ltd, Mangion Building, New Street Off Valletta Road, Luqa LQA 6000, Malta or on phone number 00356 23976000 or email at rp@ammangion.com

Company contact points

If you have further questions or require additional information, please contact Ms Gaby Ganado on +356 2397 6000 or gganado@ITS.jnj.com

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