Janssen Sciences Ireland UC

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PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA An tÚdarás Rialála Táirgí Sláinte Health Products Regulatory Authority

3rd November 2022

IMBRUVICA® (ibrutinib): New risk minimisation measures, including dose modification recommendations, due to the increased risk for serious cardiac events

Dear Healthcare Professional,

Janssen-Cilag International NV in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- **Ibrutinib increases the risk of fatal and serious cardiac arrhythmias and cardiac failure.**
- **Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of cardiac events including sudden fatal cardiac events.**
- **Prior to initiating ibrutinib, clinical evaluation of cardiac history and function should be performed.**
- **In patients with risk factors for cardiac events, benefits and risks should be assessed before initiating treatment with Imbruvica; alternative treatment may be considered.**
- **Patients should be carefully monitored during treatment for signs of deterioration of cardiac function and if this occurs, clinically managed.**
- **Ibrutinib should be withheld for any new onset or worsening grade 2 cardiac failure or grade 3 cardiac arrhythmias. Treatment may be resumed as per new dose modification recommendations (details below).**

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Background on the safety concern

Ibrutinib is indicated:

- as a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- as a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy.
- as a single agent for the treatment of adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib in combination with rituximab is indicated for the treatment of adult patients with WM.

Assessment of data from the randomised clinical trials (RCT) pool of ibrutinib showed a nearly 5-fold higher crude incidence of sudden cardiac death, sudden death, or cardiac death in the ibrutinib arm (11 cases; 0.48%) versus the comparator arm (2 cases; 0.10%). When adjusted for exposure, a 2-fold increase in the incidence rate (EAIR, expressed as number of subjects with events divided by patient-months at risk) of events of sudden cardiac death, sudden death or cardiac death was observed in the ibrutinib arm (0.0002) versus the comparator arm (0.0001).

Based on an assessment of available data on the cardiotoxicity of ibrutinib, further measures to minimize the cardiac risk have been implemented in the product information. Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events.

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating Imbruvica. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and if this occurs, clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns.

For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with Imbruvica; alternative treatments may be considered.

Section 4.4 of the SmPC has been updated accordingly and cardiac arrest has been added as an ADR in Section 4.8 of the SmPC – see https://www.medicines.ie/medicines/imbruvica-140-mg-280-mg-420-mg-and-560-mg-film-coated-tablets-34809/spc#tabs>.

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In addition, the MAH reviewed clinical data for patients experiencing Grade 3+ cardiac events and assessed whether toxicities recurred for patients who dose reduced IMBRUVICA® versus patients who did not dose reduce subsequent to these toxicities. Analyses indicate a lower incidence of recurrence of cardiac events for patients who dose-reduced IMBRUVICA® compared to those who did not reduce the dose of IMBRUVICA®.

On this basis, section 4.2 of the EU SmPC is being updated with new recommendations as follows:

Imbruvica therapy should be withheld for any new onset or worsening grade 2 cardiac failure or grade 3 cardiac arrhythmias. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), resume IMBRUVICA® therapy at the recommended dose as per the table below:

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/WM dose modification after recovery
Grade 2 cardiac failure	First	Restart at 420 mg daily	Restart at 280 mg daily
	Second	Restart at 280 mg daily	Restart at 140 mg daily
	Third	Discontinue IMBRUVICA®	
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily*	Restart at 280 mg daily*
	Second	Discontinue IMBRUVICA®	
Grade 3 or 4 cardiac failure	First	Discontinue IMBRUVICA®	
Grade 4 cardiac arrhythmias			

* Evaluate the benefit-risk before resuming treatment.

Recommended dose modifications for non-cardiac events (grade ≥3 non-haematological toxicity, grade ≥3 neutropenia with infection or fever, or grade 4 haematological toxicities) remain mainly unchanged with the addition of the following footnote in the table: "When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg".

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Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system via HPRA Pharmacovigilance, website: www.hpra.ie. Suspected adverse reactions should be reported to the HPRA via:

- Completing the online form: https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form
- Telephoning (01) 676 4971
- By downloading the form at http://www.hpra.ie/homepage/medicines/safety-information/reporting-suspected-side-effects and emailing it to medsafe@hpra.ie or post it to Freepost, Pharmacovigilance Sections, Health Products Regulatory Authority, Earlsfort Centre, Earlsfort Terrace, Dublin 2, DO2 XP77

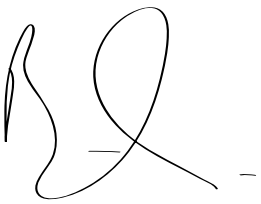
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset dates, treatment dates, product brand name and batch numbers.

Suspected adverse reactions should also be reported to Janssen on tel.: 0044(0)1494 567447, fax: +44(0)1494 567799 or by e-mail at dsafety@its.jnj.com.

Company contact point

If you have further questions, please do not hesitate to contact the Janssen Medical Information department on tel.: +1 800 709122 or email: medinfo@its.jnj.com

Kind regards,



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