Direct Healthcare Professional Communication

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 <National Competent Authority > 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).**

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 <add link to published SmPC>.*

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 Grade 4 cardiac arrhythmias	First	discontinue Imbruvica	

† 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".

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with the use of Imbruvica in accordance with the national spontaneous reporting system. *<include the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>*

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address (company contact point in the EU Member State should be included, respectively)>

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	IMBRUVICA (ibrutinib)
Marketing authorisation holder(s)	Janssen-Cilag International N.V.
Safety concern and purpose of the communication	Increased risk of fatal and serious cardiac arrhythmias and cardiac failure and related Product Information updates concerning risk factors for, and monitoring and management of cardiac toxicities, and dose modification recommendations.
DHPC recipients	Haematologists, oncologists, cardiologists and any other relevant target groups like hospital pharmacists as agreed at national level
Member States where the DHPC will be distributed	All member states where Imbruvica is authorized in the European Economic Area (EEA).

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	29 Sep 2022
DHPC and communication plan (in English) agreed by CHMP	14 Oct 2022
Submission of translated DHPCs to the national competent authorities for review	21 Oct 2022
Agreement of translations by national competent authorities	28 Oct 2022
Dissemination of DHPC	03 Nov 2022