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November 3, 2022

Subject: IMBRUVICA® (ibrutinib) Data Sheet Updates to Dose Modifications for Adverse Reactions and to Warnings and Precautions

Dear Healthcare Professional,

The purpose of this letter is to inform you of important updates to the "Dose modification guidelines" subsection of section of "4.2 Dose and method of administration" and "Cardiac arrhythmias and cardiac failure" subsection of section "4.4 Special warnings and precautions for use "of the New Zealand IMBRUVICA® Data Sheet.

IMBRUVICA® is a Bruton Tyrosine Kinase inhibitor approved for the treatment of:

- patients with MCL who have received at least one prior therapy
- patients with CLL/SLL
- patients with CLL with deletion 17p
- patients with Waldenström's macroglobulinemia (WM)

Please refer to the full IMBRUVICA® Data Sheet available at:
https://www.janssen.com/newzealand/sites/www_janssen_com_newzealand/files/prod_files/live/imbruvica_data_sheet.pdf

Background:

The updated dose modification recommendations for adverse reactions described below may reduce the occurrence of additional serious events and are intended to improve tolerability for continued IMBRUVICA® treatment.

Section 4.2: Dose and method of administration - Dose modifications guidelines

IMBRUVICA® therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade ≥ 3 non hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities.

Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), resume IMBRUVICA® therapy at the recommended dose as per the tables below.

Table 1: Recommended dose modifications for events of cardiac failure or cardiac arrhythmias

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/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.

Table 2: Recommended dose modifications for non-cardiac events:

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/WM dose modification after recovery
Grade 3 or 4 non-haematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 haematological toxicities	First*	Restart at 560 mg daily	Restart at 420 mg daily
	Second	Restart at 420 mg daily	Restart at 280 mg daily
	Third	Restart at 280 mg daily	Restart at 140 mg daily
	Fourth	Discontinue IMBRUVICA®	

*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.

Summary of updated dose modification recommendations:

- For patients experiencing Grade 2 cardiac failure, resume IMBRUVICA® treatment at a lower dose (i.e., reduce daily dose by 140 mg).
- For patients experiencing Grade 3 cardiac arrhythmias, evaluate the benefit-risk, and if resuming IMBRUVICA® treatment, re-start at a lower dose (i.e., reduce daily dose by 140 mg).
- For patients experiencing Grade 3 or 4 cardiac failure or Grade 4 cardiac arrhythmias, discontinue IMBRUVICA® at first occurrence.
- For patients experiencing Grade 3 or 4 non-cardiac events, when resuming IMBRUVICA® treatment, evaluate benefit-risk and re-start at the same or lower dose (i.e., reduce daily dose by 140 mg).

In addition, section 4.4 Special warnings and precautions for use - Cardiac arrhythmias and cardiac failure has been revised to provide additional information on cardiac arrhythmias, cardiac failure, and sudden fatal cardiac events, including a description of risk factors and guidelines for assessment and management to help prescribers better manage patients at risk.

Based on currently available evidence, Janssen maintains that the benefit-risk profile for ibrutinib remains positive when used according to the Data Sheet.

Advice to Healthcare Professionals:

- Healthcare Professionals should review and follow the updates to the IMBRUVICA® New Zealand Data Sheet, including the updated dose modification recommendations for adverse reactions.

This letter is not intended as a complete description of the benefits and risks related to the use of IMBRUVICA®. Please refer to the full Data Sheet and Consumer Medicine Information for all current updates.

Reporting Adverse Events:

Janssen is committed to monitoring the safety of our products. We encourage healthcare professionals to report any suspected adverse events for our products to the Centre for Adverse Reactions Monitoring via either their online reporting form, available at https://nzphvc.otago.ac.nz/report/, by phone on 03 479 7247 or by email at carmnz@otago.ac.nz.

If you have further questions, please contact Janssen Medical Information on 0800 800 806 or via email at medinfo@janau.jnj.com.

Sincerely

Sophie Glover-Koudounas

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