Important Safety Information on IMBRUVICA (ibrutinib) and the Risk of Serious and Fatal Cardiac Arrhythmias or Cardiac Failure

2022/08/29

Audience
Healthcare professionals including emergency room physicians, hematologists and hematologist-oncologists.

Key messages

- **IMBRUVICA (ibrutinib) was authorized by Health Canada on November 17, 2014. IMBRUVICA is used to treat adults with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM) and chronic graft versus host disease (cGVHD).**
- **Serious and fatal events of cardiac arrhythmia or cardiac failure have been reported in patients treated with IMBRUVICA. Patients with significant cardiac co-morbidities may be at greater risk for developing these events, including sudden fatal cardiac events. Related warnings have been in the Canadian Product Monograph (CPM) since authorization.**
- **Responding to data from new clinical trials and the ongoing monitoring of product safety, the CPM for IMBRUVICA has been updated to include stronger warnings on these cardiac-related events and new dose modification guidelines.**
- **Healthcare professionals are advised to:**
  - **Clinically evaluate patients' cardiac function and consider cardiac history prior to initiating IMBRUVICA therapy.**
  - **Closely monitor patients for clinical signs of cardiac function deterioration during treatment, and manage appropriately. Consider further evaluation (e.g., electrocardiogram, echocardiogram) for patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness) or new onset of dyspnea.**
  - **Follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure (see the Information for healthcare professionals section).**

What is the issue?
Serious and fatal events of cardiac arrhythmia or cardiac failure have occurred in patients treated with IMBRUVICA.

Products affected
IMBRUVICA (ibrutinib), 140 mg, 280 mg, 420 mg and 560 mg tablets, and 140 mg capsules.

Background information
IMBRUVICA (ibrutinib) was authorized by Health Canada on November 17, 2014. IMBRUVICA is used to treat adults with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM) and chronic graft versus host disease (cGVHD). Refer to the IMBRUVICA Canadian Product Monograph (CPM) for full indications.

Serious and fatal events of cardiac arrhythmia or cardiac failure have occurred in patients treated with IMBRUVICA. Patients with significant cardiac co-morbidities may be at greater risk for developing these events, including sudden fatal cardiac events. Related warnings have been in the Canadian Product Monograph (CPM) since authorization.

Responding to data from new clinical trials and ongoing monitoring of product safety, the CPM for IMBRUVICA has been updated to include stronger warnings on these cardiac-related events and new dose modification guidelines.

Among the 4,896 patients who received IMBRUVICA in clinical trials, which included patients who received IMBRUVICA in unapproved monotherapy or combination regimens, cardiac-related deaths or sudden deaths were reported in 1% of patients.

Of the 4,896 patients, 0.2% reported Grade ≥3 ventricular tachyarrhythmias, 3.7% reported Grade ≥3 atrial fibrillation and atrial flutter, and 1.3% reported Grade ≥3 cardiac failure. These events occurred particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus and a previous history of cardiac arrhythmia.

New guidelines for IMBRUVICA dose modification or treatment discontinuation due to cardiac arrhythmia or cardiac failure have been added to the IMBRUVICA CPM. These dose modification guidelines are intended to improve tolerability for continued IMBRUVICA treatment and may reduce the occurrence of additional serious events.

Information for consumers
IMBRUVICA is used to treat adults with certain types of cancer (chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma and Waldenström's macroglobulinemia) and chronic graft versus host disease.

IMBRUVICA may cause heart problems like arrhythmia (i.e., irregular heart rhythm) or heart failure (i.e., the heart does not pump blood as well as it should). These heart problems may be severe and can cause death. The risks are higher in patients who already have heart problems, high blood pressure or diabetes.

Patients should contact their healthcare professional if they experience symptoms of arrhythmia (e.g., palpitations, light-headedness, dizziness, shortness of breath, chest discomfort and fainting) or heart failure (e.g., breathlessness, difficulty breathing when lying down, swelling of the feet, ankles or legs and weakness/tiredness).

Information for healthcare professionals
Healthcare professionals are advised to:

- Clinically evaluate patients' cardiac function and consider cardiac history prior to initiating IMBRUVICA therapy.
- Closely monitor patients for clinical signs of cardiac function deterioration during treatment, and manage appropriately. Consider further evaluation (e.g., electrocardiogram, echocardiogram) for patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness) or new onset of dyspnea.
- Follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure.

<u>New dose modification guidelines</u>

IMBRUVICA therapy should be withheld for any new onset or worsening Grade 2 cardiac failure or Grade 3 cardiac arrhythmia. Once the symptoms of toxicity have resolved to Grade 1 cardiac failure or Grade 2 or lower cardiac arrhythmia, IMBRUVICA therapy can be restarted at the recommended dose, as described in the following dosage adjustment table:

Events	**Toxicity occurrence**	**CLL/WM/cGVHD dose modification after recovery**	**MCL/MZL dose modification after recovery**
Grade 2 cardiac failure	First	restart at 280 mg daily	restart at 420 mg daily
	Second	restart at 140 mg daily	restart at 280 mg daily
	Third	discontinue IMBRUVICA	
Grade 3 cardiac arrhythmias	First	restart at 280 mg daily[†]	restart at 420 mg daily[†]
	Second	discontinue IMBRUVICA	
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	discontinue IMBRUVICA	
[†] Evaluate the benefit-risk before restarting treatment.			

Action taken by Health Canada
Janssen Inc., in collaboration with Health Canada, has updated the CPM for IMBRUVICA to include new warnings regarding serious and fatal events of cardiac arrhythmia or cardiac failure, including new dose modification guidelines.

Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns
Managing marketed health product-related side effects depends on healthcare professionals and consumers reporting them. Any case of cardiac arrhythmia or cardiac failure, or other serious or unexpected side effects in patients receiving IMBRUVICA, should be reported to Janssen Inc. or Health Canada.

Janssen Inc.
19 Green Belt Drive
Toronto, ON
M3C 1L9
CANADA
Telephone:1-866-825-7122 (toll free)
Fax: 1-866-767-5865
Email: dsscan@its.jnj.com

To correct your mailing address or fax number, contact Jansen Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate
E-mail: mhpd-dpsc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

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