Johnson&Johnson

28 January 2025

IMBRUVICA® (ibrutinib):
Newly Identified Risk of Hepatotoxicity (including hepatic failure) in Warnings & Precautions section of the IMBRUVICA NZ Data Sheet and Consumer Medicine Information

Dear Healthcare Professional,

Janssen-Cilag Pty Ltd (Johnson & Johnson Innovative Medicine - 'J&J IM'), in consultation with Medsafe, would like to inform you of updates to the "Warnings and Precautions" section of the New Zealand Data Sheet and Consumer Medicine Information for IMBRUVICA.

Summary

Hepatotoxicity (including hepatic failure) has been reported in patients treated with IMBRUVICA.

Background

A recent cumulative review of data from clinical trials, post-marketing cases and literature by J&J IM has identified a causal association between the use of IMBRUVICA and hepatotoxicity (including hepatic failure).

As the evidence supports a causal association between the use of IMBRUVICA and hepatotoxicity (including hepatic failure), J&J IM has submitted a request to Medsafe to update the NZ Data Sheet and Consumer Medicine Information for IMBRUVICA to reflect this new safety information and include the clinical recommendations indicated below.

Recommendations

- Prescribers should discuss with patients the risks associated with the use of IMBRUVICA including Hepatotoxicity.

- Liver function should be assessed before initiating treatment with IMBRUVICA and patients should be monitored periodically for changes in liver function parameters during treatment.

- For patients diagnosed with hepatic events, consider consulting a liver disease expert for management.

Advice to Healthcare Professionals

- Healthcare Professionals should continue to review and follow the updates to the IMBRUVICA New Zealand Data Sheet.

- This letter is not intended as a complete description of the benefits and risks related to the use of IMBRUVICA. Healthcare Professionals should review and follow the updates to the IMBRUVICA New Zealand Data Sheet.

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J&J IM maintains that the benefit: risk balance of IMBRUVICA remains positive when used in the approved indications.

Please refer to the IMBRUVICA Data Sheet for complete prescribing information, available from the Janssen website:

https://www.janssen.com/newzealand/sites/www_janssen_com_newzealand/files/prod_files/live/imbruvica_data_sheet.pdf

Adverse Event Reporting

J&J IM is committed to monitoring the safety of our products. We encourage Healthcare Professionals to report any suspected adverse events and other safety information for IMBRUVICA to Medsafe at www.medsafe.govt.nz/safety/report-a-problem.asp and/or the J&J IM Medical Information Department.

If you have any questions, please contact J&J IM on 0800 800 806 or medinfo@janau.jnj.com.

Yours sincerely,

Michael Eisbacher

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IMBRUVICA® (ibrutinib) Minimum Datasheet

Indications:

IMBRUVICA is indicated for the treatment of: patients with CLL/SLL; patients with CLL with 17p deletion; patients with MCL who have received at least one prior therapy; patients with Waldenström's macroglobulinemia (WM).

Dosage:

IMBRUVICA should be administered orally once daily with water. IMBRUVICA can be taken with or without food. IMBRUVICA must not be taken with grapefruit juice or Seville Oranges. IMBRUVICA should continue until disease progression or no longer tolerated by the patient. **For Mantle Cell Lymphoma:** the recommended dose of IMBRUVICA for MCL is 560 mg once daily; **For Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma/ Waldenström's macroglobulinemia (CLL/SLL/WM)**: the recommended dose of IMBRUVICA for CLL/SLL/WM is 420 mg once daily. Can be taken as a single agent, or in combination with rituximab for WM. Can be taken with bendamustine and rituximab or with rituximab, *venetoclax*, *or* obinutuzumab for CLL/SLL. Administer IMBRUVICA before rituximab or obinutuzumab if given on same day. In combination with venetoclax, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax. For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily. For patients with moderate liver impairment, the recommended dose is 140mg daily. Monitor patients for signs of ibrutinib toxicity and follow

dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

Interactions:

Concomitant use of IMBRUVICA and drugs that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and should be avoided. See full PI for list. Avoid concomitant use of strong CYP3A inducers such as carbamazepine, rifampicin, phenytoin and St. John's Wort.

Contraindications:

IMBRUVICA is contraindicated in patients who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation. Use of St John's Wort is contraindicated in patients treated with IMBRUVICA.

Precautions:

Bleeding-related events Consider risks and benefits of concomitant anticoagulants/antiplatelets and monitor for signs and symptoms of bleeding. Fish oil and vitamin E preparations should be avoided; **cardiac events** atrial fibrillation, flutter ventricular tachyarrhythmia and cardiac failure including some fatal events have been reported in patients treated with ibrutinib particularly in patients with acute infections, or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Perform appropriate clinical evaluation of cardiac history and function prior to initiating IMBRUVICA. During treatment, monitor for and clinically manage signs of cardiac function deterioration. Consider further evaluation (e.g., ECG, echocardiogram), in patients whom there are cardiovascular concerns **leukostasis** isolated cases of leukostasis reported in patients treated with ibrutinib; **infections** were observed in patients treated with ibrutinib including cases of hepatitis E. Patients should be monitored for fever, vomiting, jaundice, abnormal liver function tests and confusion and appropriate anti-infective therapy should be instituted as indicated; **progressive multifocal leukoencephalopathy (PML)** cases of PML have occurred in patients treated with ibrutinib. Monitor patients for signs of PML; **cytopenias** treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Monitor complete blood counts monthly; **tumour lysis syndrome** patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment monitor patients closely; **interstitial lung disease (ILD)**; monitor patients for pulmonary symptoms indicative of ILD; **cerebrovascular accidents** cases of cerebrovascular accident, transient ischemic attack and ischemic stroke including fatalities have been reported with the use of ibrutinib, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring of patients is needed; **non melanoma skin cancer** monitor patients regularly for non-melanoma skin cancers; **hepatic events** cases of hepatotoxicity, hepatitis B reactivation, hepatitis E and hepatic failure, including fatal events, have occurred in patients treated with ibrutinib, assess liver function status before ibrutinib initiation and monitor signs and symptoms and periodically for changes in liver function parameters during treatment, a liver disease expert should be consulted for patients diagnosed with hepatic events and patients with hepatitis B serology indicative of prior infection; **hypertension** monitor blood pressure.

Pregnancy category D. IMBRUVICA should not be used during pregnancy. Women should avoid being pregnant for up to 3 months after ending IMBRUVICA treatment. Men should be advised not to father a child or donate sperm during and for 3 months after ending IMBRUVICA treatment. **Breastfeeding** breastfeeding should be discontinued during IMBRUVICA treatment.

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Adverse Reactions:

Very common (≥10%): diarrhoea, vomiting, stomatitis, nausea, constipation, abdominal pain, gastrooesphageal reflux disease, muscle spasms, cough, conjunctivitis, insomnia, anxiety, dyspepsia, bronchitis, influenza, hypokalaemia, pneumonia, upper respiratory tract infection, sinusitis, hypertension, neutropenia, thrombocytopenia, anaemia, rash, myalgia, arthralgia, back pain, pain in extremity, musculoskeletal pain, fatigue, dizziness, headache; contusion, neuropathy peripheral, asthenia, haemorrhage, bruising, pruritus, dry skin, petechiae, pyrexia, peripheral oedema, hyperuricaemia, dehydration, decreased appetite, dyspnoea, oropharyngeal pain, nasal congestion, epistaxis, atrial fibrillation, urinary tract infection, skin infection; dry eye, vision blurred, lacrimation increased, visual acuity reduced, chills, blood creatinine increased, hypoalbuminaemia, skin cancer, arthropathy, pain. Common (≥ 1%): hyponatremia, platelets decreased, haemoglobin decreased, hypocalcaemia, bilirubin increased, hyperkalaemia, AST increased, ALT increased, creatinine clearance decreased, febrile neutropenia, leucocytosis, lymphocytosis, subdural haematoma, sepsis, non melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma. See full Datasheet for other Adverse Effects.

Presentation:

90 and 120 capsule bottle or 30 tablet blister (140 mg, 280 mg, 420 mg and 560 mg) or 120 tablet pack (140 mg only) Store below 30°C.
IMBRUVICA (ibrutinib) is funded for CLL/SLL post relapse on venetoclax. IMBRUVICA is an unfunded medicine for MCL and WM – a co-payment for the medicine and prescription charges will apply.

Before prescribing please review full Data Sheet (available from https://www.janssen.com/newzealand/sites/www_janssen_com_newzealand/files/prod_files/live/imbruvica_data_sheet.pdf .

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