AUTHORIZATION WITH CONDITIONS OF IMBRUVICA® (ibrutinib) for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL)

July 28, 2015

Dear Healthcare Professional(s),

Janssen Inc. is pleased to announce that Health Canada has issued a Notice of Compliance with Conditions under the Notice of Compliance with Conditions (NOC/c) policy for IMBRUVICA® (ibrutinib) capsules for the treatment of patients with relapsed or refractory mantle cell lymphoma (MCL).

Health Canada has issued a marketing authorization with conditions under the NOC/c policy for IMBRUVICA® to reflect the promising nature of the clinical data of IMBRUVICA® in patients with this serious disease and the need for further follow-up to verify the clinical benefit. Products authorized under Health Canada's NOC/c policy have demonstrated promising benefit, are of high quality, and possess an acceptable safety profile based on a benefit/risk assessment.

As part of its conditions Janssen Inc. has undertaken to provide Health Canada with final analysis reports for the following studies:

- PCYC-1104-CA, a phase 2 study of ibrutinib in relapsed or refractory MCL (based on 24-month duration of follow-up);
- PCI-32765MCL2001, a phase 2 study in subjects with MCL who have received at least 1 rituximab-containing chemotherapy regimen and who progressed after at least 2 cycles of bortezomib therapy;
- PCI-32765MCL3001, a randomized phase 3 study of ibrutinib versus temsirolimus in subjects with relapsed or refractory mantle cell lymphoma who have received at least 1 prior rituximab-containing chemotherapy regimen.

Authorization with conditions for IMBRUVICA® was based on the results obtained from study PCYC-1104-CA, a multicenter, single-arm, phase 2 study investigating the efficacy and safety of ibrutinib (560 milligrams once daily) given until disease progression or unacceptable toxicity in 111 patients with relapsed or refractory[1] MCL. The primary endpoint was investigator-assessed overall response rate (ORR). At median duration of follow-up of 15.3 months, the ORR was 67.6%, including a complete response rate of 20.7% and a partial response rate of 46.8%. The median time to initial response was 1.9 months, and the median duration of response (DOR) was estimated to be 17.5 months.

Indications and Clinical Use:
IMBRUVICA® (ibrutinib) has been issued market authorization with conditions for the treatment of patients with relapsed or refractory MCL.

Patients should be advised about the conditional market authorization for this indication.

Other Approved Indications for IMBRUVICA®:
IMBRUVICA® (ibrutinib) has been issued marketing authorization without conditions for the treatment of patients with chronic lymphocytic leukemia (CLL), including those with 17p deletion, who have received at least one prior therapy, or for the frontline treatment of patients with CLL with 17p deletion.

Action and Clinical Pharmacology:
Ibrutinib is a small-molecule, targeted inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to inhibition of BTK enzymatic activity.

Serious Warnings and Precautions:
IMBRUVICA® should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents. The following are serious warnings and precautions to be taken into consideration regarding the use of IMBRUVICA®:

- Major hemorrhagic events (Grade ≥3), including subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural haemorrhage have been reported. The mechanism for the bleeding events is not well understood.
- IMBRUVICA® should not be used in patients with moderate or severe hepatic impairment.
- IMBRUVICA® should not be used concomitantly with a strong CYP3A inhibitor (see **Drug Interactions**, below).

For further details, see the IMBRUVICA® Product Monograph.

[1] Patients enrolled into study PCYC-1104-CA had documented failure to achieve at least partial response with, or documented disease progression after the most recent treatment regimen.

Adverse Reactions:
The adverse reactions described below reflect exposure of patients with MCL to IMBRUVICA® with median treatment duration of 8.3 months. The most common adverse reactions (≥20%) were diarrhea, fatigue, nausea, peripheral edema, dyspnea, constipation, upper respiratory tract infection, vomiting and decreased appetite, and thrombocytopenia. The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, thrombocytopenia, anemia, pneumonia, diarrhea, abdominal pain, hyperuricemia, fatigue, and atrial fibrillation. Approximately 10% of patients discontinued treatment due to adverse events. Adverse events leading to dose reduction occurred in approximately 14% of patients. Isolated cases of leukostasis have been observed.

Drug Interactions:
Concomitant use of IMBRUVICA® and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure significantly and should be avoided. Grapefruit and Seville oranges must not be consumed during IMBRUVICA® treatment, as they contain moderate inhibitors of CYP3A. If concomitant use of a strong CYP3A inhibitor is necessary, withhold treatment with IMBRUVICA® for the duration of inhibitor use. If concomitant use of a moderate CYP3A inhibitor is necessary, reduce IMBRUVICA® dose for the duration of inhibitor use.

Concomitant use of IMBRUVICA® and drugs that strongly induce CYP3A decreases ibrutinib exposure and should be avoided.

IMBRUVICA® may increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin. Dose reduction of these concomitant drugs may be necessary.

IMBRUVICA® may increase the absorption of BCRP and P-gp substrates. Therefore, narrow therapeutic range BCRP and P-gp substrates, such as methotrexate and digoxin, respectively, should be taken at least 6 hours before or after IMBRUVICA® to avoid a potential interaction in the GI tract.

Dosage and Administration:
IMBRUVICA® should be administered orally, with or without food, with a glass of water once daily, at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA® must not be taken with grapefruit juice. Treatment with IMBRUVICA® should continue until disease progression or until no longer tolerated by the patient.

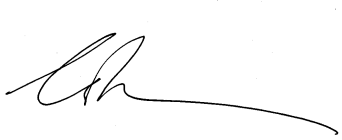
Upon initiation of treatment with IMBRUVICA®, a reversible increase in lymphocyte counts, often associated with reduction of lymphadenopathy, has been observed in most patients with CLL and some patients with MCL. This lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings.

The recommended dose of IMBRUVICA® for MCL is 560 milligrams (four 140 milligram capsules) once daily, which is higher than the recommended daily dose of 420 milligrams (three 140 milligram capsules) for CLL.

For the complete prescribing information and information available for patients/caregivers, please consult the IMBRUVICA® Product Monograph. The Product Monograph is available at www.janssen.ca/product/628 or by request by contacting Janssen Inc. Medical Information at 1-800-567-3331 or 1-800-387-8781.

Access to IMBRUVICA®:
Janssen Inc. has created the YOU&i™ Support Program which offers services to patients and physicians, including patient health information and navigation of drug reimbursement options. For more information please call 1-844-888-0080 (M-F 8am-8pm EST) or visit www.janssen-youandi.ca.

Should you have medical enquiries regarding IMBRUVICA®, please contact our Medical Information Department at 1-800-567-3331 or 1-800-387-8781.



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Reporting Suspected Side Effects
Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
HEALTH CANADA
Tunney's Pasture
Address Locator: 0701C
Ottawa, Ontario
K1A 0K9
Telephone: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Telephone: 1-866-234-2345
Fax: 1-866-678-6789
Email: CanadaVigilance@hc-sc.gc.ca

The Adverse Reaction Reporting Form and the Adverse Reaction Guidelines can be found on the Health Canada website or in The Canadian Compendium of Pharmaceuticals and Specialties.

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Metabolism, Oncology and Reproductive Science
E-mail: bmors_enquiries@hc-sc.gc.ca

Telephone: 613-941-3171
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