

Ibrutinib (Imbruvica™) Criteria for Use September 2014, Update March 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vaww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive ibrutinib.*

- Care not provided by a VA or VA purchased care (e.g. Choice Program, Fee Basis) hematology/oncology provider.
- Unable to swallow oral capsules whole and intact
- Patient with history of non-adherence with oral medication, follow-up appointments or laboratory visits
- Chronic therapy with a strong CYP3A4 inhibitor that cannot be interrupted (e.g. ritonavir, nefazodone)
- Chronic therapy with strong CYP3A4 inducer that cannot be interrupted (e.g. carbamazepine, rifampin, phenytoin, St. John's Wort)
- High risk for bleeding event including oral anticoagulant therapy (see Issues for Consideration)
- Gastrointestinal condition that may interfere with ibrutinib absorption.
- Chronic or unresolved infection
- Autoimmune Hemolytic Anemia (AIHA)
- History of stroke or intracranial hemorrhage in prior 6 months
- Severe renal impairment defined as CrCl \leq 30 ml/min (drug has not been studied in this setting)
- Clinically significant cardiovascular disease such as uncontrolled arrhythmia, CHF (NYHA Class 3 or 4), MI in prior 6 months (See Issues for Consideration)
- AST (SGOT) or ALT (SGPT) \geq 3x ULN or with moderate-severe hepatic impairment (Child-Pugh B or C). (see Issues for Consideration)
- Absolute Neutrophil Count (ANC) $<$ 750 cells/ μ L, and/or platelet count $<$ 30,000 cells/ μ L unless bone marrow involvement

Inclusion Criteria *One of the following must be fulfilled in order to meet criteria.*

- Diagnosis of Mantle Cell Lymphoma (MCL) and progressive disease or intolerance to at least one prior therapy

- Diagnosis of Chronic Lymphocytic Leukemia (CLL)
 - With RELAPSED disease [patient achieved CR* or PR* on initial therapy (e.g. fludarabine, bendamustine, chlorambucil)]
 - AND progressed on retreatment with initial therapy OR is not a candidate for initial therapy

- Diagnosis of Chronic Lymphocytic Leukemia (CLL)
 - With REFRACTORY disease [patient failed to achieve CR or PR on initial therapy (e.g. fludarabine, bendamustine, chlorambucil) or developed disease progression]

- Diagnosis of Chronic Lymphocytic Leukemia (CLL) as FRONT-LINE THERAPY in patients who have acceptable indications for treatment only AND one of the following:
 - Laboratory-confirmed chromosome 17p deletion
 - Patient is NOT a candidate for anti-CD20 therapy (i.e. rituximab, obinutuzumab, ofatumumab)
 - Patient is NOT a candidate for purine analog therapy

- Diagnosis of Waldenstrom's Macroglobulinemia (WM) and progressive disease or intolerance to at least one prior therapy

AND

- Goals of care and role of Palliative Care consult have been discussed and documented.

- ECOG* Performance Status 0 - 2

For women of childbearing potential

- Pregnancy should be excluded prior to receiving ibrutinib and the patient provided contraceptive counseling on potential risk vs. benefit of taking ibrutinib if patient were to become pregnant

September 2014, March 2016

Updated versions may be found at <http://www.pbm.va.gov> or <https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx>

*CR Complete Response; PR Partial Response; ECOG Eastern Cooperative Oncology Group

Dosage and Administration

- MCL dose is 560 mg (4 x 140 mg capsules) orally once daily with a glass of water.
- CLL and WM dose is 420 mg (3 x 140 mg capsules) orally once daily with a glass of water.
- The recommended dose for patients with mild liver impairment (Child-Pugh class A) is 140 mg daily (one capsule).
- Use of ibrutinib should be avoided in patients with moderate or severe hepatic impairment (Child-Pugh class B or C)
- Due to a 2-fold increase in ibrutinib exposure when taken with food, take drug 30 minutes prior to or 2 hours after a meal.
- Capsules should not be opened, broken or chewed.
- Missed doses should be taken as soon as possible on the same day; return to usual schedule the following day; do not take extra doses on subsequent days to make up for a missed dose.
- Use appropriate precautions for handling and disposal. Ibrutinib is considered a hazardous agent.

Monitoring

- Symptoms of arrhythmia, such as palpitations, lightheadedness, dizziness, fainting or new onset dyspnea
- Renal function at baseline and each month. Maintain/encourage adequate hydration
- CBC with differential at baseline and each month
- LFTs at baseline and as clinically indicated
- Unusual bleeding and/or bruising
- Fever and signs/symptoms of infection
- Severity and duration of diarrhea
- Evidence of disease response or progression (via radiographic scan or symptomatology)

Issues for Consideration

- Fludarabine and bendamustine each have efficacy and safety data to support their use in CLL, therefore they should be given consideration in patients with refractory disease prior to ibrutinib.
- Ibrutinib may increase risk of bleeding in patients receiving antiplatelet or anticoagulant therapies. Grade 3 or higher bleeding events have occurred in up to 6% of patients. All Grades of bleeding (including bruising) were reported in 48% of MCL patients and 63% of CLL patients. Patients receiving anticoagulation with warfarin were excluded from clinical trials.
- Consider risk vs. benefit of holding ibrutinib for 3-7 days pre- and post-surgical procedures depending on type of surgery and risk of bleeding.
- Fish-oil supplements were thought to contribute to grade 2 epistaxis events during the WM trial, as the events resolved when the supplements were discontinued.
- Elderly patients (age ≥ 65 years) experienced more Grade 3 adverse events in the clinical trial setting, especially cardiac events and infection. Use caution and intense monitoring in these Veterans.
- Consider risks vs. benefits of ibrutinib in any patient with paroxysmal or persistent atrial fibrillation. Atrial fibrillation and atrial flutter have occurred particularly in patients with cardiac risk factors, acute infections and a prior history of afib.
- Patients with AST (SGOT) or ALT (SGPT) $\geq 3x$ ULN were excluded from clinical trials. In a hepatic impairment trial, a single dose increased AUC and C_{max} in patients with mild, moderate and severe hepatic impairment. Dose reduction is recommended in patients with mild impairment. Those with moderate/severe impairment should not receive ibrutinib. Concomitant ketoconazole (strong CYP3A4 inhibitor) therapy, in healthy volunteers, increased ibrutinib C_{max} and AUC by 29x and 24x respectively. Avoid concomitant administration of ibrutinib with moderate or strong CYP3A4 inhibitors. If concomitant therapy with a moderate CYP3A4 inhibitor cannot be avoided, dose-reduce ibrutinib to 140 mg daily. Interrupt ibrutinib for short-term use of CYP3A4 inhibitors (e.g. antifungals or antibiotics for ≤ 7 days). A 7-day interruption in ibrutinib therapy did not compromise efficacy.
- Avoid grapefruit and Seville oranges (both contain moderate inhibitors of CYP3A4)

Discontinuation Recommendations

- Non-compliance with therapy, laboratory or follow-up requests
- Decline in ECOG performance status to level unacceptable for patient to maintain quality of life
- Persistent or recurring toxicity despite two dose-reductions
- Evidence of progressive disease (note: lymphocytosis should not be considered as disease progression, as this may be an effect of ibrutinib therapy)

Prepared: September 2014, Updated March 2016. Contact: Berni Heron, VA Pharmacy Benefits Management Services