IBRU Regimen
Ibrutinib

Disease Site  Hematologic - Leukemia - Chronic Lymphocytic (CLL)

Intent  Palliative

Regimen Category  Evidence-Informed:
Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses
- For the treatment of patients with chronic lymphocytic leukemia (CLL), including those with 17p deletion, who have received at least one prior therapy, including those with 17p deletion.
- For the treatment of previously untreated CLL patients, including those with 17p deletion.

Note:
Trial data in previously untreated CLL patients with 17p deletion is very limited.

Supplementary Public Funding  iBRUtinib
Exceptional Access Program (iBRUtinib - For patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to specific criteria.) (EAP Website)
B - Drug Regimen

**iBRUtinib**

420 mg PO Daily

(Outpatient prescription in multiples of 140 mg capsules)

C - Cycle Frequency

**CONTINUOUS TREATMENT**

Until disease progression or unacceptable toxicity.

D - Premedication and Supportive Measures

**Antiemetic Regimen:** Minimal – No routine prophylaxis; PRN recommended

**Other Supportive Care:**

- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.
- Consider prophylaxis for patients at an increased risk for opportunistic infections.
- Ibrutinib may be affected by CYP3A inducers and inhibitors; see Drug Interaction section for dose adjustments.

Also refer to [CCO Antiemetic Recommendations](#).

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The
following recommendations have been adapted from clinical trials or product monographs and may be considered. Patients who require anticoagulant treatment should not start ibritinib until they are stable on their anticoagulant. Do not use warfarin or other vitamin K antagonists concomitantly with ibritinib.

**Dosage with toxicity**

In the phase 3 clinical trial, ibritinib was discontinued for any toxicity lasting longer than 28 days.

<table>
<thead>
<tr>
<th>Toxicity Occurrence</th>
<th>CLL dose modification after recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Restart at 420 mg daily</td>
</tr>
<tr>
<td>2nd</td>
<td>Restart at 280 mg daily</td>
</tr>
<tr>
<td>3rd</td>
<td>Restart at 140 mg daily</td>
</tr>
<tr>
<td>4th</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Ibrutinib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 ANC &gt; 7 days OR Grade ≥3 neutropenia with infection or fever OR Grade 4 platelets or thrombocytopenic bleeding</td>
<td>Hold until ≤ grade 1, restart at dose indicated above</td>
</tr>
<tr>
<td>Grade 3 or 4 non-hematologic toxicity (despite appropriate treatment)</td>
<td>Hold until ≤ grade 1, restart at dose indicated above</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Lymphocytes &gt; 400,000/mcL</td>
<td>Consider temporary hold. Monitor closely for signs of leukostasis and manage patient appropriately.</td>
</tr>
<tr>
<td>New onset or inadequately controlled hypertension</td>
<td>Initiate or adjust antihypertensive treatment as appropriate.</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
<td>Consider risk vs. benefit of continuing treatment</td>
</tr>
<tr>
<td>Surgery</td>
<td>Hold 3-7 days pre and post-surgery depending on the surgery type and risk of bleeding, restart at physician discretion</td>
</tr>
<tr>
<td>Concomitant usage of CYP3A inhibitors</td>
<td>See Drug Interactions section for specific dose modifications</td>
</tr>
<tr>
<td>PML</td>
<td>Hold and investigate. Discontinue if confirmed.</td>
</tr>
<tr>
<td>New or worsening respiratory symptoms</td>
<td>Hold, manage appropriately and investigate for ILD. Discontinue if confirmed.</td>
</tr>
</tbody>
</table>
Hepatic Impairment

Ibrutinib is metabolised in the liver and increased exposure has been demonstrated in patients with hepatic impairment. The risk of bleeding increases in moderate to severe hepatic impairment. Patients with AST/ALT ≥ 3 × ULN were excluded from clinical trials.

Suggested Dose Modifications:

<table>
<thead>
<tr>
<th>Hepatic impairment</th>
<th>Ibrutinib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Class A</td>
<td>140 mg daily (if benefits of treatment outweigh risks)</td>
</tr>
<tr>
<td>Child-Pugh Class B or C</td>
<td>Do not start ibrutinib</td>
</tr>
</tbody>
</table>

Renal Impairment

Ibrutinib has minimal renal clearance.

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Ibrutinib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>No change; monitor creatinine</td>
</tr>
<tr>
<td>≤ 30 or dialysis</td>
<td>No data</td>
</tr>
</tbody>
</table>

Dosage in the Elderly

No difference in effectiveness of ibrutinib was observed for patients over 65 years of age compared to younger patients. Steady state drug levels are higher in the elderly, but no starting dosage adjustment is required. Grade 3 or higher adverse events (including fatal events) occurred more frequently, including anemia, pneumonia, atrial fibrillation, hypertension, peripheral edema, infections (e.g. pneumonia, urinary tract infections and cellulitis) and GI effects (e.g. diarrhea and dehydration).
### F - Adverse Effects

Refer to ibrutinib drug monograph(s) for additional details of adverse effects

<table>
<thead>
<tr>
<th>Very common (≥ 50%)</th>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytosis (including leucostasis)</td>
<td>Diarrhea (may be severe)</td>
<td>Rash</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fever</td>
<td>Fever</td>
<td>Increased LFTs</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>Myelosuppression +/- infection, bleeding (may be severe)</td>
<td>Myelosuppression +/- infection, bleeding (may be severe)</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Mucositis</td>
<td>Mucositis</td>
<td>Tumour lysis syndrome</td>
</tr>
<tr>
<td>Edema</td>
<td>Constipation</td>
<td>Constipation</td>
<td>Secondary malignancy (non-melanoma skin cancer)</td>
</tr>
<tr>
<td>Cough, dyspnea</td>
<td>Headache</td>
<td>Headache</td>
<td>Leukoencephalopathy (PML)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Dizziness</td>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
<td>Blurred vision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Hypertension (may be severe)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GERD</td>
<td>GERD</td>
<td></td>
</tr>
</tbody>
</table>

### G - Interactions

Refer to ibrutinib drug monograph(s) for additional details

- Ibrutinib is primarily metabolized by CYP3A.
- For strong CYP3A inhibitors:
  - Avoid concomitant use, where possible. If not possible to avoid, hold ibrutinib for duration of inhibitor use ≤ 7 days.
- For moderate CYP3A inhibitors:
  - Reduce ibrutinib dose to 140 mg daily for duration of inhibitor use.
- For strong CYP3A inducers, avoid concomitant use, where possible. May co-administer with mild inducers.
- Avoid anticoagulants and antiplatelet medications if possible. Do not use concomitant warfarin.
H - Drug Administration and Special Precautions

Refer to ibrutinib drug monograph(s) for additional details

Administration:

- Administer ibrutinib orally, with or without food, with a glass of water once daily, at approximately the same time each day. Do not open, break or chew the capsules.
- Avoid grapefruit and Seville orange juice during treatment.
- If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day. Return to the regular dosing schedule the following day. Do not take extra capsules to make up for a missed dose.
- Store at room temperature (15-30°C)

Contraindications:

- Patients who have a hypersensitivity to this drug or to any of its components
- Patients with moderate or severe hepatic impairment
- Do not use concomitantly with strong CYP3A inhibitors (refer to Interactions section)
- Do not use warfarin or other vitamin K antagonists concomitantly with ibrutinib

Special Precautions:

- Should not be used in patients with moderate or severe hepatic impairment
- Do not use concomitantly with strong CYP3A inhibitors or warfarin like anticoagulants (refer to Interactions section)
- Major bleeding events have been reported. Exercise caution in patients at risk of bleeding, including those receiving concomitant antiplatelet therapy or anticoagulants.
- Exercise caution in patients with cardiac risk factors, history of atrial fibrillation or acute infection.
- Use with caution in patients with high tumour burden due to risk of TLS
- Hold for 3 to 7 days pre and post-surgery

Pregnancy and Lactation:
I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and monthly
- Liver function tests; baseline and at each visit
- Renal function tests; baseline and at each visit
- Blood pressure; baseline and at each visit
- Coagulation parameters; baseline and as clinically indicated, more frequent in patients at risk of bleeding
- Clinical toxicity assessment for infection, leucostasis, TLS, bleeding, GI, cardiac and respiratory effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

ECG in patients with cardiac risk factors, history of atrial fibrillation or acute infection; Baseline and as clinically indicated

J - Administrative Information

Outpatient prescription for home administration

K - References

Ibrutinib drug monograph, Cancer Care Ontario.

**June 2019 Updated emetic risk category**

**M - Disclaimer**

**Regimen Abstracts**

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

**Regimen Monographs**

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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