Regimen Monograph

A - Regimen Name

IBRU Regimen

Ibrutinib

Disease Site

Hematologic
Lymphoma - Non-Hodgkin's Low Grade

Waldenström's macroglobulinemia

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 Waldenström's macroglobulinemia (WM)

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B - Drug Regimen

iBRUtinib	420 mg	PO	Daily

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- 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.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients who require anticoagulant treatment should not start ibrutinib until stable coagulation is achieved.

Ibrutinib should be held 3-7 days pre- and post-surgery depending on the surgery type and risk of bleeding; restart at physician discretion.

Ibrutinib may be affected by CYP3A inducers and inhibitors; see Drug Interaction section for dose adjustments.

Dosage with toxicity

Dose Level	Ibrutinib Dose (mg/day)
0	420
-1	280
-2	140
-3	Discontinue

Dose Modifications for Non-cardiac toxicity:

Toxicity / Occurrence		Action
Hypertension		Initiate or adjust antihypertensive treatment as appropriate.
Grade 4 hematologic toxicity OR Grade ≥ 3 neutropenia with infection or fever OR Grade ≥ 3 non-hematologic toxicity	1st occurrence	Hold*, resume at same dose or consider 1 dose level ↓.
	2nd and 3rd occurrence	Hold*, resume at 1 dose level ↓.
	4th occurrence	Discontinue.
Major hemorrhage		Discontinue.
Lymphocytes > 400,000/microlitre		Consider temporary hold. Monitor closely for signs of leukostasis and manage patient appropriately.
Symptoms of PML (e.g. weakness, confusion)		Hold and investigate. Discontinue if confirmed for any grade.
Symptoms of ILD/Pneumonitis (treatment-related)		Hold and investigate. Discontinue if confirmed for any grade

*Do not restart until hematological and non-hematological toxicities resolve to ≤ grade 1 or baseline.

Dose Modifications for Cardiac toxicity:

Toxicity / Occurrence		**Action**
Grade 2 heart failure	1st occurrence	Hold*; resume at 1 dose level ↓
	2nd occurrence	Hold*; resume at 1 dose level ↓
	3rd occurrence	Discontinue
Grade ≥ 3 heart failure		Discontinue
Grade 3 arrhythmia	1st occurrence	Hold**; resume at 1 dose level ↓
	2nd occurrence	Discontinue
Grade 4 arrhythmia		Discontinue

*Do not restart until heart failure resolves to ≤ grade 1 or baseline.
**Consider risk vs. benefit before restarting treatment.

Hepatic Impairment

Ibrutinib is metabolized in the liver and increased exposure is seen in patients with hepatic impairment. The risk of bleeding increases in moderate to severe hepatic impairment.

Hepatic Impairment	**Ibrutinib Dose**
Mild (Child-Pugh class A)	140 mg daily (if benefits of treatment outweigh risks)
Moderate or Severe (Child-Pugh class B or C)	Do not use.

Renal Impairment

Ibrutinib has minimal renal clearance.

Creatinine Clearance (mL/min)	Ibrutinib Starting Dose
> 30	No dose adjustment during clinical trials.
≤ 30	No data.

Dosage in the Elderly

No dose adjustment required. No difference in effectiveness of ibrutinib was observed for patients with B-cell malignancies ≥ 65 years of age compared to younger patients. Steady state drug levels are higher in the elderly, but no starting dosage adjustment is required. Patients ≥ 65 years of age reported more frequent grade 3 or higher adverse events (including fatal events), as well as thrombocytopenia, pneumonia, hypertension, urinary tract infection, and atrial fibrillation.

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F - Adverse Effects

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

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe) • Musculoskeletal pain • Fatigue	• Anorexia • Cough, dyspnea • Nausea, vomiting • Rash (may be severe) • Edema • Dry eye • Constipation • Myelosuppression ± infection, bleeding (including opportunistic, hepatitis B and other viral reactivation) (may be severe) • Headache • Hypertension (may be severe) • Mucositis • Visual disorders (may be severe) • Watering eyes • Dizziness • Dyspepsia	• Arterial thromboembolism • Atrial fibrillation • Arrhythmia • PR interval prolonged • Cardiotoxicity • Hepatic failure • Cirrhosis • Renal failure • Hypersensitivity • Lymphocytosis (including leukostasis) • Tumor lysis syndrome • Secondary malignancy (non-melanoma skin cancer, non-skin cancer) • Hemorrhage • Leukoencephalopathy (PML) • Interstitial lung disease

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G - Interactions

Refer to ibrutinib drug monograph(s) for additional details.

- For strong CYP3A inhibitors, avoid concomitant use due to ↑ ibrutinib exposure; if unavoidable short term (≤ 7 days), hold* ibrutinib for duration of inhibitor use.
- For moderate CYP3A inhibitors (excluding voriconazole), reduce* ibrutinib dose to 280 mg daily for duration of inhibitor use due to ↑ ibrutinib exposure.
- For voriconazole, reduce* ibrutinib dose to 140 mg for duration of inhibitor use due to ↑ ibrutinib exposure.
- For strong CYP3A inducers, avoid concomitant use due to ↓ ibrutinib exposure.
- Caution with the concurrent use of ibrutinib and anticoagulants or drugs that inhibit platelet function. If anticoagulation is required, consider temporary hold of ibrutinib until stable anticoagulation achieved.
- Avoid supplements that may inhibit platelet aggregation (e.g. fish oil, flaxseed, vitamin E).
- PGP substrates (e.g. verapamil, digoxin) and BRCP substrates (e.g. methotrexate) with narrow therapeutic range must be taken ≥ 6 hours before or after the ibrutinib dose. BCRP substrates may require dose reduction.

**Resume previous dose of ibrutinib after strong or moderate CYP3A inhibitor discontinuation.*

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H - Drug Administration and Special Precautions

Refer to ibrutinib drug monograph(s) for additional details.

Administration

- Administer ibrutinib with or without food.
- Swallow whole with a glass of water. Do not open, break or chew capsules.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during ibrutinib treatment.

- If a dose of ibrutinib is missed, patient may take it as soon as possible on the same day and return to the scheduled time the next day. Patient should not take an extra dose to make up for a missed dose.

- Store at room temperature (15-30^{o}C).

Contraindications

- Patients who have a hypersensitivity to this drug or any components of the formulation.

Warnings/Precautions

- Do not use ibrutinib in patients with moderate or severe hepatic impairment due to ↑ risk of coagulopathy and bleeding. Patients with AST/ALT ≥ 3 x ULN were excluded from clinical trials.

- Avoid concomitant use of ibrutinib with strong CYP3A inhibitors due to ↑ ibrutinib exposure.

- Exercise caution in patients at risk of bleeding, including those receiving anticoagulants or medications that inhibit platelet function. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Patients on warfarin or other vitamin K antagonists and those with a history of recent stroke or intracranial hemorrhage were excluded from clinical trials. Patients with congenital bleeding conditions have not been studied.

- Exercise caution in patients with cardiac risk factors, hypertension, pre-existing conduction system abnormalities, history of arrhythmias/atrial fibrillation or acute infection.

- Transient lymphocytosis has been observed in patients treated with ibrutinib and should not be considered progressive disease in the absence of other clinical findings.

- Patients should use caution when driving or operating a vehicle or potentially dangerous machinery due to fatigue, dizziness and asthenia.

Pregnancy/Lactation

- Ibrutinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.

- Women who use hormonal contraception should add a barrier method. Male patients should use a condom and not donate sperm during treatment, and for at least **3 months** after the last dose.

- Breastfeeding is not recommended during treatment and for **1 week** after the last dose.

- Fertility effects: Unknown

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and monthly
- Liver function tests; Baseline and at each visit
- Renal function tests; Baseline and as clinically indicated
- Blood pressure; Baseline and at each visit
- Coagulation parameters; Baseline and as clinically indicated, more frequent in patients at risk of bleeding
- Heart failure and arrhythmia assessment; baseline and as clinically indicated
- ECG in patients with cardiac risk factors, history of atrial fibrillation, acute infection, or who develop arrhythmic symptoms; Baseline and as clinically indicated
- Clinical toxicity assessment for infection, hepatitis B reactivation, leukostasis, TLS, bleeding, GI, cardiovascular, neurologic and respiratory effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Ibrutinib drug monograph, Ontario Health (Cancer Care Ontario).

Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015 Apr 9;372(15):1430-40.

February 2023 Updated dose modifications section

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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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