Drug Monograph

A - Drug Name

iBRUtinib

COMMON TRADE NAME(S): Imbruvica®

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B - Mechanism of Action and Pharmacokinetics

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) that prevents B-cell activation and signaling.

Absorption	Rapidly absorbed after oral administration. Exposure increases with doses up to 840mg.	
	Bioavailability	3% (fasted condition); 8% (with a meal)
	Effects with food	Administration with a high-fat breakfast increased AUC by 2-fold and C_{max} up to 4.5-fold
	Peak plasma levels	1 to 2 hours (~2 to 4 hours with food)
Distribution	PPB	97%
	Cross blood brain barrier?	Yes
Metabolism	Main enzymes involved	CYP3A major, CYP2D6 minor
	Active metabolites	Yes
	Inactive metabolites	Yes

Elimination	Feces	80%, 1% as unchanged drug
	Urine	< 10%
	Half-life	4-6 hours

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C - Indications and Status

Health Canada Approvals:

- Chronic lymphocytic leukemia (CLL)
- Waldenstrom macroglobulinemia (WM)
- Mantle cell lymphoma (MCL)
- Marginal zone lymphoma (MZL)
- Chronic graft vs. host disease (cGVHD)

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Diffuse large B cell lymphoma (DLBCL)

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were reported in a phase 3 study of ibrutinib 420 mg in previously untreated patients with CLL or SLL. It also includes severe or life-threatening adverse effects from other sources or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (including ventricular tachyarrhythmias) (rare)	E
	Arterial thromboembolism (rare)	E
	Atrial fibrillation (6%) (11% in MCL, 5% in WM)	E
	Cardiotoxicity (1%) (severe)	E
	Hypertension (14%) (4% severe)	E D
	PR interval prolonged (rare)	E
Dermatological	Nail disorder (onychoclasis; common from clinical trials)	E
	Rash (21%) (including Stevens-Johnson syndrome) (may be severe)	E
Gastrointestinal	Anorexia (24%) (MCL)	E
	Constipation (16%)	E
	Diarrhea (42%) (4% severe)	E
	Dyspepsia (11%)	E
	Mucositis (14%)	E
	Nausea, vomiting (22%)	I E
General	Edema - limbs (19%)	E
	Fatigue (30%)	E
Hematological	Hemorrhage (3%) (severe)	E
	Myelosuppression ± infection, bleeding (16%) (including opportunistic infections, viral reactivation; 10% severe)	E
	Other (≤69%) Lymphocytosis (35% in MCL, 11% in MZL, < 1% in WM); leukostasis-rare	E
Hepatobiliary	Cirrhosis (rare) (may be severe)	E
	Hepatic failure (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (7%) (↓ Na; 3% severe)	E
	Tumour lysis syndrome (rare)	E

Musculoskeletal	Musculoskeletal pain (36%)	E
Neoplastic	Secondary malignancy (6%) (non-melanoma skin cancers, 4% non-skin related)	D L
Nervous System	Dizziness (11%)	E
	Headache (14%)	E
	Leukoencephalopathy (PML - rare)	E
	Peripheral neuropathy	E
Ophthalmic	Dry eye (17%)	E
	Visual disorders (13%) (including ≤ 5% cataracts, unilateral blindness; may be severe)	E
	Watering eyes (13%)	E
Renal	Renal failure (rare) (may be severe)	E
Respiratory	Cough, dyspnea (22%)	E
	Interstitial lung disease (2%)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ibrutinib include lymphocytosis, diarrhea, musculoskeletal pain, fatigue, cough, dyspnea, nausea, vomiting, rash, edema (limbs), dry eye and constipation.

Atrial fibrillation, atrial flutter, heart failure, and **arrhythmias** (including fatal events) were reported, particularly in patients with cardiac risk factors, hypertension, diabetes, acute infection, and a previous history of cardiac arrhythmias.

Cerebrovascular accident, transient ischemic attack, and ischemic stroke (including fatalities) have been reported, with and without concomitant atrial fibrillation and/or hypertension; causality with ibrutinib has not been established.

In the pooled safety database, grade 3 or 4 **hypertension** has occurred with a median time to onset of 6 months. Increased incidence has been observed over time while on treatment with ibrutinib.

Transient lymphocytosis (≥ 50% increase from baseline) was observed in most CLL patients treated with ibrutinib with a median time to onset of 1 to 2 weeks and a median time to resolution of 12 to 14 weeks. When given in combination with obinutuzumab or in combination with bendamustine and rituximab, the incidences were lower and median times to resolution were shorter. The increase in lymphocytes may be related to a pharmacodynamic effect of BTK inhibition and should not be considered progressive disease in the absence of other clinical signs.

Rare cases of **leukostasis** have occurred within two to three weeks of starting treatment and included intracranial hemorrhage, lethargy, gait instability and headache. Risk increases in patients with circulating lymphocytes > 400,000/microlitre.

BTK is expressed in platelets and ibrutinib inhibits collagen-induced platelet aggregation in vitro. Major **hemorrhage** has been reported, including subdural hematoma and deaths. Patients > 65 years of age, receiving concomitant antiplatelet or anticoagulant drugs, with a history of bleeding disorders, thrombocytopenia or leukocytosis, or who have had recent strokes or intracranial hemorrhage are at increased risk and should be monitored closely.

Cases of **progressive multifocal leukoencephalopathy (PML)** have been reported.

Cases of **hepatitis B viral reactivation** have also been reported, although causality has not been established.

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E - Dosing

Refer to protocol by which patient is being treated.

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

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.

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.

Adults:

For CLL, WM or cGVHD:

Oral: 420 mg once daily

For MCL or MZL:

Oral: 560 mg once daily

For combination regimens, refer to the regimen monographs or the ibrutinib product monograph for more information.

Dosage with Toxicity:

Dose Level	Ibrutinib Dose (mg/day)	
	CLL or WM or cGVHD	MCL or MZL
0	420	560
-1	280	420
-2	140	280
-3	Discontinue	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.

Dosage with 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.

For B-cell malignancies:

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.

For adult cGVHD:

Hepatic Impairment*	Ibrutinib Dose
bilirubin >1.5 to 3 x ULN	140 mg daily (if benefits of treatment outweigh risks)
bilirubin > 3 x ULN	Do not use.

*unless of non-hepatic origin or due to Gilbert's Syndrome.

Dosage with 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 is 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.

Children:

Ibrutinib is indicated in pediatric patients ≥ 1 year of age with cGVHD after failure of one or more lines of systemic therapy. Refer to the product monograph for details.

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F - Administration Guidelines

- Administer ibrutinib with or without food.
- Swallow whole with a glass of water. Do not open, break or chew capsules.
- Consider giving ibrutinib prior to rituximab or obinutuzumab when used in combination.
- 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).

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G - Special Precautions

Contraindications:

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

Other 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.
- 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 and dizziness.

Pregnancy and Lactation:

- Genotoxicity: No
- Clastogenicity: No
- Fetotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Pregnancy:
  - Ibrutinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **3 months** after the last dose.
  - Patients who use hormonal contraception should add a barrier method.
  - Patients who produce sperm should use a condom and not donate sperm during treatment, and for **3 months** after the last dose.
- Fertility effects: Unlikely
  Not demonstrated in animal studies; no data in humans.
- Breastfeeding:
  - Breastfeeding is not recommended during treatment and for **1 week** after the last dose.

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H - Interactions

Ibrutinib is primarily metabolized by CYP3A.

In vitro, ibrutinib is an inhibitor of P-gp and BCRP transporters and a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 enzymes. Inhibition or induction of CYP450 enzymes by ibrutinib or its metabolites is unlikely to result in clinically significant drug interactions with CYP450 substrates.

In vitro, ibrutinib is a substrate of OCT2*;* administration of P-gp or other major transporter inhibitors is unlikely to lead to clinically relevant interactions.

Co-administration with grapefruit juice increased exposure. Grapefruit and Seville oranges should be avoided during treatment.

No dose adjustment is required when used with mild CYP3A4 inhibitors.

Concomitant medications that ↑ stomach pH (e.g., proton pump inhibitors) were permitted in the pivotal clinical trials.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inhibitors (e.g. ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole, cobicistat) or Posaconazole (excluding patients with cGVHD)	↑ ibrutinib exposure (up to 26x with ketoconazole)	↓ ibrutinib metabolism	• Avoid; consider an alternative with less CYP3A inhibition. • If co-administration is unavoidable short term (≤ 7 days), hold ibrutinib for duration of inhibitor use.*
Moderate CYP3A inhibitors (e.g. erythromycin, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) (Excluding voriconazole - see next page)	↑ ibrutinib exposure	↓ ibrutinib metabolism	For B-Cell Malignancies: • ↓ ibrutinib dose to 280 mg for duration of inhibitor use.* For cGVHD: • No dose adjustment required.
Posaconazole (in patients with cGVHD) Dose > 200 mg BID (suspension) or > 300 mg QD (delayed release tablet) or 300 mg QD (IV)	↑ ibrutinib exposure	↓ ibrutinib metabolism	• Avoid; consider an alternative with less CYP3A inhibition. • If co-administration is unavoidable short term (≤ 7 days), hold ibrutinib for duration of inhibitor use.*

Posaconazole (in patients with cGVHD) Dose ≤ 200 mg BID, as suspension	↑ ibrutinib exposure	↓ ibrutinib metabolism	• ↓ ibrutinib dose to 280 mg for duration of inhibitor use.*
Posaconazole (in patients with cGVHD) Dose 300 mg QD, as delayed release tablet	↑ ibrutinib exposure	↓ ibrutinib metabolism	• ↓ ibrutinib dose to 140 mg for duration of inhibitor use.*
Voriconazole	↑ ibrutinib exposure	↓ ibrutinib metabolism	For B-Cell Malignancies: • ↓ ibrutinib dose to 140 mg for duration of inhibitor use.* For cGVHD: • ↓ ibrutinib dose to 280 mg for duration of inhibitor use.*
Strong CYP3A inducers (e.g. phenytoin, rifampin, carbamazepine, St. John's Wort, etc) or Moderate CYP3A inducers (e.g. efavirenz)	↓ ibrutinib exposure (up to 10x with rifampin)	↑ ibrutinib metabolism	• Avoid strong CYP3A inducers • Consider an alternative with less CYP3A induction. May co-administer with mild inducers.
P-glycoprotein substrates (e.g. digoxin, aliskiren, fexofenadine)	↑ P-gp substrate exposure and/or toxicity (theoretical)	Ibrutinib inhibits P-gp *in vitro*	• Narrow therapeutic range P-gp substrates should be taken at least 6 hours before or after ibrutinib.

BCRP substrates (e.g. topotecan, methotrexate, imatinib, rosuvastatin)	↑ BCRP substrate exposure and/or toxicity (theoretical)	Ibrutinib inhibits BCRP *in vitro*	• Narrow therapeutic range BCRP substrates should be taken at least 6 hours before or after ibrutinib. • BCRP substrates may require dose reduction.
Anticoagulants or antiplatelets	↑ risk of bleeding	Additive	• Caution. If required, consider temporary hold of ibrutinib until stable anticoagulation achieved.
Supplements that may inhibit platelet aggregation (e.g. fish oil, flaxseed, vitamin E)	↑ risk of bleeding	Additive	• Avoid.
Drugs that prolong the PR interval (e.g. beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, antiarrhythmics and HIV protease inhibitors)	↑ risk of toxicity	Additive	• Caution.

*Resume previous ibrutinib dose after inhibitor discontinuation.

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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

Monitor Type	Monitor Frequency
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, secondary malignancy, 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 - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- iBRUtinib - For patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to specific criteria.
- iBRUtinib - For relapsed and refractory Mantle Cell Lymphoma, according to clinical criteria
- iBRUtinib - For the treatment of patients with relapsed or refractory Waldenström Macroglobulinemia, in combination with rituximab, based on criteria.
- iBRUtinib - For the treatment of patients with relapsed or refractory Waldenström Macroglobulinemia, as monotherapy, based on criteria

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K - References

Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373(25):2425-2437.

Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014 Jul 17;371(3):213-23.

Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016 Feb;17(2):200-11.

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June 2025 Updated Dosing, Pregnancy/Lactation, and Monitoring sections

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L - Disclaimer

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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