DRUG NAME: Ibrutinib

SYNONYM(S): PCI-32765[1]

COMMON TRADE NAME(S): IMBRUVICA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Ibrutinib is a small-molecule, irreversible inhibitor of Bruton's tyrosine kinase (BTK).[2] BTK is an integral part of the B-cell antigen receptor (BCR) pathway, which is associated with the pathogenesis of several B-cell malignancies, including chronic lymphocytic leukemia (CLL). Ibrutinib inhibits malignant B-cell proliferation and survival as well as reduces cell migration and substrate adhesion.[3]

PHARMACOKINETICS:

Oral Absorption[3,4]	rapid absorption; time to peak 1-2 h; administration with food increases C_{max} and AUC 2-fold	
Distribution	widely distributed[5]	
	cross blood brain barrier?	no information found
	volume of distribution	10,000 L
	plasma protein binding	~97%
Metabolism	primarily by hepatic metabolism via CYP 3A	
	active metabolite(s)	dihydrodiol metabolite (PCI-45227)[4]
	inactive metabolite(s)	M25; M34; M21
Excretion	mainly fecal excretion	
	urine	<10%
	feces	80%; 1% as unchanged drug
	terminal half life	4-6 h; half life of dihydrodiol metabolite is 6-11 h
	clearance	1000 L/h
Elderly	higher AUC and C_{max} of ibrutinib and dihydrodiol metabolite	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic lymphocytic
*Lymphoma, mantle cell
*Lymphoma, non-Hodgkin's
*Waldenstrom's macroglobulinemia

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***Hemorrhagic events*** are reported; use with caution in patients taking anticoagulants or medications that inhibit platelet function. Hold treatment for 3-7 days pre- and post-surgery; reinitiate post-surgery based on the risk of bleeding.[3]
- ***Atrial fibrillation, atrial flutter,*** and ***ventricular tachyarrhythmias*** are reported; use with caution in patients with cardiac risk factors, acute infections, or a history of arrhythmias.[6]
- Ibrutinib causes a dose- and concentration-dependent ***prolongation of PR interval;*** monitor ECG in patients with pre-existing conduction abnormalities (e.g., AV block) or tachyarrhythmias.[6]
- ***Hyperuricemia*** and ***tumour lysis syndrome*** have been reported with ibrutinib treatment.[3]
- ***Hepatitis B reactivation*** has been reported with ibrutinib[6]; HBV screening (HBsAg and anti-HBc) is suggested prior to initiation of ibrutinib; if either test is positive, prophylaxis with lamivudine 100 mg/day orally is indicated during treatment with ibrutinib and for 6 months after.[7-9]

Special populations: Elderly patients (≥ 65 years) experience more cardiac events (atrial fibrillation, hypertension), infections (pneumonia, cellulitis), gastrointestinal events (diarrhea, dehydration), as well as a higher frequency of grade 3 or greater adverse effects.[3,4]

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary malignancies and skin cancer have been reported in patients treated with ibrutinib.[3]

Mutagenicity: Not mutagenic in Ames test. Ibrutinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: No fertility studies have been conducted. In animal toxicology studies, ibrutinib did not have an adverse effect on reproductive organs.[3]

Pregnancy: FDA Pregnancy Category D.[2] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
In animal studies, increased post-implantation loss, visceral malformations, and decreased fetal weights have been reported. It is unknown if ibrutinib is present in semen. Effective contraception is recommended during treatment and for 3 months after treatment.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[10,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (23-44%, severe 5-10%)[2,3,5]
	febrile neutropenia (2%, severe 2%)
	leukocytosis (4%, severe 3%)
	lymphocytosis (4%, severe 2%); see paragraph following **Side Effects** table
	neutropenia (22-54%, severe 12-29%)[2,3,5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	thrombocytopenia (17-71%, severe 5-17%)[2,3]
cardiac	***atrial fibrillation/flutter*** (5-9%, severe 3%)[2,3]; see paragraph following **Side Effects** table
	ventricular tachyarrhythmia[6]; see paragraph following **Side Effects** table
eye	blurred vision (10%)
gastrointestinal	*emetogenic potential:* low[12]
	abdominal pain (15-24%, severe 5%)[2]
	constipation (15-25%, severe 2%)[2,3]
	diarrhea (48-63%, severe 4-5%)[2,3]
	dyspepsia (11-13%)[2]
	nausea (21-31%, severe 2%)[2,3]
	stomatitis (17-21%, severe 1%)[2,3]
	vomiting (14-23%, severe 2%)[2,3]
general disorders and administration site conditions	asthenia (13-14%, severe 3-4%)[2]
	chills (13%)[2]
	fatigue (28-41%, severe 2-5%)[2,4]
	peripheral edema (21-35%, severe 3%)[2,5]
	pyrexia (18-27%, severe 1-2%)[2,3,5]
infections and infestations	***hepatitis B reactivation***[6]
	infections (64%, severe 21-26%); severe infections occurred most frequently within the first 6 months of treatment[2,3,5]
	pneumonia (10-15%, severe 6-17%)[2,3,5]
	sepsis (4%, severe 2%)
	skin infections (7-17%, severe 2-6%)[2,3]
	sinusitis (11-21%, severe 1-6%)[2,3]
	upper respiratory tract infection (16-48%, severe 1-2%)[2,3]
	urinary tract infection (10-14%, severe 3-4%)[2,3]
injury, poisoning, and procedural complications	bruising (11-54%, severe 2%)[2-4]
	laceration (10%, severe 2%)[2,4]
	subdural hematoma (1-2%)[3,4]
investigations	creatinine increase (9%)[2]
metabolism and nutrition	appetite decrease (17-21%, severe 2%)[2]
	dehydration (12%, severe 4-6%)[2,5]
	hyperuricemia (13-40%)[2]; see paragraph following **Side Effects** table
musculoskeletal and connective tissue	arthralgia (11-27%, severe 1%)[2,3,5]
	musculoskeletal pain (27-37%, severe 1-6%)[2,3]
	muscle spasms (14-19%, severe 2%)[2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
neoplasms	***secondary malignant neoplasm*** (1-10%)[2-4]
	skin cancer, non-melanoma (4-8%)[2,4]
nervous system	dizziness (11-21%)[2,3]
	headache (13-19%, severe 1-2%)[2,3]
	peripheral neuropathy (10%)[2]
	progressive multifocal leukoencephalopathy[6]
psychiatric	anxiety (10%)[2]
	insomnia (10%)[2]
renal and urinary	renal failure (<1%)[2]
respiratory, thoracic and mediastinal	cough (19-31%)[2,5]
	dyspnea (10-27%, severe 4%)[2]
	epistaxis (9-11%)[2,3]
	oropharyngeal pain (15%)[2]
skin and subcutaneous tissue	petechiae (11-17%)[2,3]
	rash (24-27%, severe 3%)[2,3]
vascular	***hemorrhage*** (48-63%,severe 3-6%)[2,3,13]; see paragraph following **Side Effects** table
	hypertension (17%, severe 8-14%)[2,5]

Adapted from standard reference[3] unless specified otherwise.

A temporary ***lymphocytosis*** is reported with ibrutinib, usually occurring within the first few weeks of therapy. Eighty percent of affected patients will achieve resolution in 8-23 weeks. This increase in lymphocyte counts (≥50% increase from baseline and above absolute lymphocyte count of 5,000/mcL) may be due to the inhibition of BTK-mediated cellular homing and adhesion and should not be considered disease progression in the absence of other clinical findings. Rare cases of leukostasis (lymphocytes >400,000/mcL) have also been reported; administer supportive care as needed and consider temporarily interrupting ibrutinib therapy.[2,3,14]

Atrial fibrillation, atrial flutter, and ***ventricular tachyarrhythmia*** are reported. Ibrutinib also causes a dose and concentration-dependent prolongation of the PR interval. Ibrutinib should be used with caution in patients with pre-existing arrhythmias, cardiac risk factors, or conduction abnormalities. An ECG is recommended in patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea. If arrhythmias persist, consider dose reduction or discontinuation of treatment.[6]

Hyperuricemia may result from cell lysis by ibrutinib and may lead to electrolyte disturbances or acute renal failure.[15] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[16]:

- aggressive hydration: 3 L/m^2/24 hr with target urine output>100 mL/h
- if possible, discontinue drugs that cause hyperuricemia(e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg PO initially, then 300 mg PO q6h x 6 doses, then 300 mg PO daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric

acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[17] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[18]

Minor ***hemorrhagic events*** (e.g., bruising, epistaxis, and petechiae) occur in approximately half of the patients treated with ibrutinib, both with and without thrombocytopenia. Major hemorrhagic events, such as subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural bleeding are reported in 3% of patients. Bruton's tyrosine kinase is expressed in platelets; however, the mechanism for bleeding events is not well understood. Patients using concomitant antiplatelet or anticoagulant agents are reported to have more minor bleeding events compared to those without. If therapeutic anticoagulation is required, consider temporarily withholding ibrutinib treatment until stable anticoagulation is achieved. Avoid using supplements that may also have an inhibitory effect on platelet aggregation, such as fish oil, flaxseed, and vitamin E preparations. Moderate to severe hepatic impairment may also increase risk of bleeding as hepatic dysfunction is associated with coagulopathy. In addition, ibrutinib should be temporarily withheld in patients requiring surgery (i.e., at least 3 to 7 days pre- and post-surgery), and reinitiated post-surgery depending upon the type of surgery and the risk of bleeding.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[3,19]	may increase plasma level of ibrutinib	may inhibit CYP 3A metabolism of ibrutinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with ibrutinib
ketoconazole[3]	increased ibrutinib C_{max} and AUC (by 29- and 26-fold, respectively)	strong inhibition of CYP 3A by ketoconazole	if concomitant use is unavoidable, hold ibrutinib for duration of treatment with ketoconazole
rifampin[3,4]	decreased ibrutinib C_{max} and AUC (by 13- and 10-fold, respectively)	strong induction of CYP 3A by rifampin	avoid concomitant use if possible

Ibrutinib is a substrate of CYP 3A4. Concomitant therapy with strong or moderate **CYP 3A inhibitors** may increase ibrutinib exposure; avoid if possible. For short-term (7 days or less)[4,13] concomitant use with a *strong* CYP 3A inhibitor, hold ibrutinib for duration of CYP 3A inhibitor therapy. If concomitant use with a *moderate* CYP 3A inhibitor is necessary, suggest ibrutinib dose reduction to140 mg daily. No ibrutinib dose adjustment is recommended for concomitant therapy with *mild* CYP 3A inhibitors; monitor for ibrutinib toxicity. Concomitant use of ibrutinib with a *strong* **CYP 3A inducer** may decrease ibrutinib exposure; avoid if possible. Ibrutinib may be given concomitantly with *mild* CYP 3A inducers.[3]

Ibrutinib is an inhibitor of P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP) and may increase serum levels of P-gp and BCRP substrates; clinical significance is unknown. Suggest spacing concomitant therapy with substrates having a narrow therapeutic index by 6 hours, before or after ibrutinib.[3,4]

SUPPLY AND STORAGE:

Oral: Janssen Inc. supplies ibrutinib as 140 mg hard gelatin capsules. Store at room temperature.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[6,8,9]: ***420-560 mg*** (range 140-560 mg) ***PO once daily***

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure[3]: no adjustment recommended in mild or moderate renal impairment; no information found for severe renal impairment

Dosage in hepatic failure[3]:

degree of hepatic impairment	recommended dose
mild (Child-Pugh A)	140 mg PO daily; monitor patient for signs of toxicity
moderate or severe (Child-Pugh B or C)	not recommended; hepatic impairment is associated with coagulopathy and may increase the risk of bleeding

Dosage in dialysis: no information found

Children: no information found

REFERENCES:

1. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31(1):88-94.
2. Lexi-Drugs® (database on the Internet). Ibrutinib. Lexi-Comp Inc., 13 January 2015. Available at: http://online.lexi.com. Accessed 13 January 2015.
3. Janssen Inc. IMBRUVICA® product monograph. Toronto, Ontario; 14 November 2014.
4. Pharmacyclics Inc. IMBRUVICA® full prescribing information. Sunnyvale, CA, USA; July 2014.
5. Cameron F, Sanford M. Ibrutinib: first global approach. Drugs 2014;74:263-271.
6. Janssen Inc. IMBRUVICA® product monograph. Toronto, Ontario; 24 July 2018.
7. BC Cancer Lymphoma Tumour Group. (ULYMIBRU) BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Mantle-Cell Lymphoma Using iBRUtinib. Vancouver, British Columbia: BC Cancer; 1 October 2018.
8. BC Cancer Lymphoma Tumour Group. (ULYIBRU) BC Cancer Protocol Summary for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma using IBRUtinib. Vancouver, British Columbia: BC Cancer; 1 February 2018.
9. BC Cancer Lymphoma Tumour Group. (ULYFIBRU) BC Cancer Protocol Summary for Treatment of Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with Chromosome 17p Deletion Using iBRUtinib. Vancouver, British Columbia: BC Cancer; 1 February 2018.
10. Laurie Sehn MD. Personal communication. BC Cancer Agency Lymphoma Tumour Group; 18 March 2015.
11. Linda Hamata Pharmacist. Personal communication. BC Cancer Agency Lymphoma Tumour Group; 8 April 2015.
12. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
13. Aalipour A, Advani RH. Bruton's tyrosine kinase inhibitors and their clinical potential in the treatment of B-cell malignancies: focus on ibrutinib. Ther Adv Hemtol 2014;5(4):121-133.
14. Janssen Inc. IMBRUVICA® product monograph. Toronto, Ontario; 14 September 2015.
15. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640.
16. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27.

17. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
18. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93-94.
19. MICROMEDEX® 2.0 Drug Interactions (database on the Internet). Ibrutinib. Truven Health Analytics, updated periodically. Available at: http://www.micromedexsolutions.com/. Accessed 26 January 2015.