PRODUCT MONOGRAPH

[Pr]IMBRUVICA™

ibrutinib capsules

140 mg

Bruton's Tyrosine Kinase (BTK) Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule / 140 mg	*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

IMBRUVICA™ (ibrutinib) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL), including those with 17p deletion, who have received at least one prior therapy, or for the frontline treatment of patients with CLL with 17p deletion.

Clinical effectiveness of IMBRUVICA™ in the frontline setting is based on the benefit observed in CLL patients with 17p deletion who have received at least one prior therapy. Clinical trial data in the frontline setting are very limited.

Geriatrics (≥65 years of age):
In studies of CLL patients treated with IMBRUVICA™, 60% were ≥65 years of age. No overall differences in the efficacy of IMBRUVICA™ treatment were observed between these patients and younger patients. Grade 3 or higher adverse events, serious adverse events, and fatal adverse events occurred more frequently among elderly patients treated with IMBRUVICA™ than among younger patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (<18 years of age):
The safety and efficacy of IMBRUVICA™ in children and adolescents have not been evaluated.

CONTRAINDICATIONS

IMBRUVICA™ is contraindicated in patients who have known hypersensitivity to ibrutinib or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

IMBRUVICA™ should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.

- Major bleeding events have been reported (see **Hemorrhage**, below)
- IMBRUVICA™ should not be used in patients with moderate or severe hepatic impairment (see **Special Populations**, below)
- IMBRUVICA™ should not be used concomitantly with a strong CYP3A inhibitor (see **Drug Interactions**, below)

General

Effects on Ability to Drive and Use Machines

Fatigue, dizziness and asthenia have been reported very commonly in patients taking IMBRUVICA™ and should be considered when assessing a patient's ability to drive or operate machines.

Carcinogenesis and Mutagenesis

Second Primary Malignancies

In the pooled safety database, other malignancies, most frequently skin cancers, occurred in 8% of patients treated with IMBRUVICA™. Non-skin related malignancies occurred in 3% of CLL patients. No carcinogenicity studies have been done.

Cardiovascular

Patients treated with IMBRUVICA™ reported events of atrial fibrillation (including Grade ≥3 events) and atrial flutter, particularly patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Atrial fibrillation was reported more frequently in the ibrutinib arm (5%; Grade 3+4, 3%) than in the comparator arm (1%; Grade 3+4, 0%) in the randomized clinical trial. Periodically monitor all patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed. For atrial fibrillation which persists, consider the risks and benefits of IMBRUVICA™ treatment and follow the dose modification guidelines (see **DOSAGE AND ADMINISTRATION**).

In a phase 2 study with limited ECG evaluations, data showed a decrease in QTcF interval by an average of 8.9 ms relative to baseline. A dedicated QT study has not been performed (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug Interactions

Concomitant use of IMBRUVICA™ and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure significantly and should be avoided (see **DRUG INTERACTIONS**). Grapefruit and Seville oranges must not be consumed during IMBRUVICA™ treatment, as they contain moderate inhibitors of CYP3A. If concomitant use of a strong CYP3A inhibitor is necessary, withhold treatment with IMBRUVICA™ for the duration of inhibitor use. If concomitant use of a moderate CYP3A inhibitor is necessary, reduce IMBRUVICA™ dose for the duration of inhibitor use (see **DOSAGE AND ADMINISTRATION**).

Concomitant use of IMBRUVICA™ and drugs that strongly induce CYP3A decreases ibrutinib exposure and should be avoided (see **DRUG INTERACTIONS**).

IMBRUVICA™ may increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin. Dose reduction of these concomitant drugs may be necessary (see **DRUG INTERACTIONS**).

IMBRUVICA™ may increase the absorption of narrow therapeutic range BCRP and P-gp substrates, such as methotrexate and digoxin, respectively, and should be taken at least 6 hours before or after IMBRUVICA™ to avoid a potential interaction in the GI tract (see **DRUG INTERACTIONS**).

Endocrine and metabolism

Tumour Lysis Syndrome

Tumour lysis syndrome has been reported with IMBRUVICA™ therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

Gastrointestinal

Diarrhea

In the pooled safety database, diarrhea occurred in 51% of patients treated with IMBRUVICA™, with Grade 3 or higher diarrhea in 4% of patients. To prevent dehydration, administer fluid and electrolyte replacement and antidiarrheal medications as needed. Follow IMBRUVICA™ dose modification guidance as needed (see **DOSAGE AND ADMINISTRATION**).

Hematologic

Cytopenias

In the pooled safety database, treatment-emergent Grade 3 or 4 cytopenias, including neutropenia (14%), thrombocytopenia (7%) and anemia (5%) were reported in patients treated with IMBRUVICA™. Patients should have their complete blood counts monitored monthly and their doses modified as necessary (see **DOSAGE AND ADMINISTRATION**).

Lymphocytosis

Upon initiation of IMBRUVICA™, a temporary increase in lymphocyte counts (≥50% increase from baseline and above absolute lymphocyte count of 5000/mcL) occurred in 70% of CLL patients; 80% of these patients achieved resolution. The median time to treatment-emergent lymphocytosis was 1.1 weeks, with a median time to resolution of approximately 14 weeks. Lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings.

Leukostasis

Isolated cases of leukostasis have been reported in patients treated with IMBRUVICA™. Cases were typically reported within two to three weeks of ibrutinib initiation, and included cases of intracranial hemorrhage, lethargy, gait instability, and headache. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. In patients with high number of circulating lymphocytes (>400,000/mcL), consider temporarily holding IMBRUVICA™ treatment, and monitor patients closely for signs of leukostasis, particularly in patients who experience a rapid increase of lymphocyte count to above 400,000/mcL. Administer supportive care including hydration and/or cytoreduction as indicated.

Hemorrhage

Major hemorrhagic events (Grade ≥3), including subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage, occurred in 3% of patients treated with IMBRUVICA™. Minor hemorrhagic events, including contusion, epistaxis, and petechiae, occurred in approximately half of the patients treated with IMBRUVICA™, both with and without thrombocytopenia. BTK is expressed in platelets; however, the mechanism for the bleeding events is not well understood.

In clinical studies, IMBRUVICA™-treated patients using concomitant antiplatelet or anticoagulant agents had more minor bleeding events compared to those without these concomitant drugs. Patients were excluded from participation in IMBRUVICA™ studies if they required warfarin or other vitamin K antagonists, or if they had a recent history of stroke or intracranial hemorrhage. Patients with congenital bleeding diathesis have not been studied.

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA™. IMBRUVICA™ should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. If therapeutic anticoagulation is required, consider temporarily withholding IMBRUVICA™ treatment until stable anticoagulation is achieved. Supplements that may have an inhibitory effect on platelet aggregation, such as fish oil, flaxseed, and vitamin E preparations, should be avoided.

IMBRUVICA™ should be held at least 3 to 7 days pre and post-surgery, and reinitiated at the discretion of the physician, depending upon the type of surgery and the risk of bleeding.

Immune

Infections

In the pooled safety database, infections (including sepsis, bacterial, viral, or fungal infections) occurred in 64% of patients treated with IMBRUVICA™, with Grade 3 or higher infections in 21% of patients, and fatal infections in 2% of patients. Most patients reporting infections, including those with fatal infections, also had neutropenia. Patients should be monitored for fever, neutropenia, and infections, and appropriate anti-infective therapy should be instituted as indicated. Follow IMBRUVICA™ dose modification guidance as needed (see **DOSAGE AND ADMINISTRATION**).

Peri-Operative Considerations

IMBRUVICA™ should be held at least 3 to 7 days pre and post-surgery depending on the type of surgery and the risk of bleeding (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Sexual Function/Reproduction

Fertility studies with ibrutinib have not been conducted. Men should be advised to not father a child while receiving IMBRUVICA™, and for 3 months following completion of treatment.

Special Populations

Pregnant Women

There are no adequate and well controlled studies of IMBRUVICA™ in pregnant women. In studies with pregnant rats, ibrutinib was associated with increased post-implantation loss, increased visceral malformations (heart and major vessels), and decreased fetal weights (see **TOXICOLOGY**). Based on these findings, IMBRUVICA™ may cause fetal harm when administered to pregnant women.

IMBRUVICA™ should not be used during pregnancy. Women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA™ and for at least 3 months after ending treatment. Women who use hormonal methods of birth control must add a barrier method. If IMBRUVICA™ is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA™, the patient should be apprised of the potential hazard to a fetus.

It is not known whether ibrutinib or its metabolites are present in semen. Male patients should use a condom if engaging in sexual activity with a pregnant woman while receiving IMBRUVICA™ and for 3 months after treatment has stopped.

Nursing Women

It is not known whether ibrutinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to

IMBRUVICA™ in nursing infants, breastfeeding should be discontinued during IMBRUVICA™ treatment.

Pediatrics (<18 years of age)

The safety and efficacy of IMBRUVICA™ in children and adolescents have not been evaluated.

Geriatrics (≥65 years of age)

Of the 442 patients treated for CLL in studies PCYC-1102-CA and PCYC-1112-CA, 60% were ≥65 years of age. No overall differences in the efficacy of IMBRUVICA™ treatment were observed between these patients and younger patients. Grade 3 or higher adverse events occurred more frequently among elderly patients treated with IMBRUVICA™ (65% of patients age ≥65 versus 53% of younger patients). Grade ≥3 serious adverse events were also reported more frequently in elderly patients than in younger patients (43% versus 33%, respectively), as were adverse events leading to drug discontinuation (11% versus 5%, respectively) and fatal adverse events (8% versus 4%, respectively). Patients ≥65 years of age also had higher steady-state systemic exposures of ibrutinib and the dihydrodiol metabolite (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥3.0x upper limit of normal (ULN) were excluded from IMBRUVICA™ clinical trials. In a dedicated study in patients with hepatic impairment, preliminary data showed a significant increase in ibrutinib exposure (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**). As hepatic impairment can lead to coagulopathy, the risk of bleeding associated with IMBRUVICA™ may be increased in patients with moderate or severe hepatic impairment. IMBRUVICA™ should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C). Preliminary pharmacokinetic data showed comparable exposures of the unbound ibrutinib in patients with mild hepatic impairment (Child-Pugh class A) administered a 140 mg dose and patients without hepatic impairment administered a 420 mg daily dose. If the benefit is considered to outweigh the risk in a patient with mild hepatic impairment, a dose reduction to 140 mg should be considered. Monitor patients for signs of toxicity (see **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Ibrutinib has minimal renal clearance. Clinical pharmacokinetic studies have not been conducted in patients with renal impairment. Patients with mild or moderate renal impairment (creatinine clearance >30 mL/min) were treated in clinical studies without adjustment of the starting dose. Hydration should be maintained and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Monitoring and Laboratory Tests

Patients should have their baseline renal function and hepatic status, and coagulation status measured prior to IMBRUVICA™ initiation. Patients with cardiac risk factors or a history of atrial fibrillation, or with acute infections should have their baseline ECG assessed prior to IMBRUVICA™ initiation.

Patients treated with IMBRUVICA™ should be monitored for symptoms of atrial fibrillation, infection, and fever, and have their complete blood counts monitored monthly. Patients with renal impairment should have their serum creatinine levels monitored periodically.

ADVERSE REACTIONS

Overview

The safety of IMBRUVICA™ has been assessed in an integrated safety population of 504 IMBRUVICA™-treated patients.

The data described below reflect exposure to IMBRUVICA™ in a controlled, randomized clinical study (Study PCYC-1112-CA) that included 195 CLL patients treated with ibrutinib who had received at least one prior therapy.

The most commonly occurring adverse reactions in the study (≥20%) were diarrhea, musculoskeletal pain, nausea, rash, pyrexia, anemia, neutropenia, and bruising (Table 1). The most common Grade 3/4 adverse reactions (≥5%) were neutropenia, pneumonia, thrombocytopenia and anemia.

Discontinuation and dose reduction due to AEs

Approximately 4% of patients receiving IMBRUVICA™ in study PCYC-1112-CA discontinued treatment due to adverse events. These adverse events included infections, diarrhea, atrial fibrillation, and subdural hematoma. Adverse events leading to dose reduction occurred in approximately 4% of patients.

Leukostasis

Isolated cases of leukostasis have been observed in IMBRUVICA™ clinical studies, including patients who developed lymphocytosis greater than 400,000/mcL and experienced intracranial hemorrhage, lethargy, gait instability, and headache (see **WARNINGS AND PRECAUTIONS, Hematologic**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions presented in this section are adverse events that were considered to be reasonably associated with the use of ibrutinib based on the comprehensive assessment of the available adverse event information. A causal relationship with ibrutinib cannot be reliably established in individual cases.

Adverse reactions described in Table 1 below reflect exposure to IMBRUVICA™ with a median duration of 8.6 months and exposure to ofatumumab with a median duration of 5.3 months in Study PCYC-1112-CA. Adverse reactions occurring at ≥10% incidence and 5% greater in the IMBRUVICA™ arm when compared to the ofatumumab arm or serious adverse reactions ≥2% incidence and 2% greater in the IMBRUVICA™ arm when compared to the ofatumumab arm or biologically plausible are presented.

Table 1: Adverse reactions reported from Study PCYC-1112-CA

	IMBRUVICA™ (N=195)		**Ofatumumab (N=191)**	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Blood and lymphatic system disorders				
Anemia	23	5	17	8
Neutropenia	22	16	15	14
Thrombocytopenia	17	6	12	4
Lymphocytosis	4	2	3	1
Leukocytosis	4	3	1	0
Febrile neutropenia	2	2	3	3
Cardiac disorders				
Atrial fibrillation	5	3	1	0
Eye disorders				
Vision blurred	10	0	3	0
Gastrointestinal disorders				
Diarrhea	48	4	18	2
Nausea	26	2	18	0
Stomatitis*	17	1	6	1
Constipation	15	0	9	0
Vomiting	14	0	6	1
General disorders and administration site conditions				
Pyrexia	24	2	15	1
Infections and infestations				
Upper respiratory tract infection	16	1	10	2
Pneumonia*	15	10	13	9

Table 1: Adverse reactions reported from Study PCYC-1112-CA

	IMBRUVICA™ (N=195)		Ofatumumab (N=191)	
System Organ Class Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Sinusitis*	11	1	6	0
Urinary tract infection	10	4	5	1
Skin infection*	7	2	3	1
Sepsis*	4	2	4	3
Injury, poisoning and procedural complications				
Subdural hematoma	1	0	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	28	2	18	1
Arthralgia	17	1	7	0
Nervous system disorders				
Headache	14	1	6	0
Dizziness	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	9	0	3	1
Skin and subcutaneous tissue disorders				
Rash*	24	3	13	0
Bruising*	21	0	4	0
Petechiae	14	0	1	0

* Includes multiple adverse reaction terms.
Patients with multiple events for a given adverse reaction term are counted once only for each adverse reaction term.
Events are sorted by system organ class and by decreasing frequency of adverse reaction term in the IMBRUVICA™ arm.

Abnormal Hematologic and Clinical Chemistry Findings

Table 2: Hematologic laboratory abnormalities (per IWCLL criteria) from Study PCYC-1112-CA

Laboratory Parameter	IMBRUVICA™ N=195		Ofatumumab N=191	
	All Grades (%)	**Grades 3 or 4 (%)**	**All Grades (%)**	**Grades 3 or 4 (%)**
Hemoglobin decreased[a]	36	0	21	0
Neutrophils decreased[b]	51	23	57	26
Platelets decreased[c]	52	5	45	10

[a] Grade 1: decreased ≥10.5% to <24.5% and <lower limit of normal (LLN); Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN.
[b] Units=$x10^9$/L; Grade 1: ≥1.5 to <2.0; Grade 2: ≥1.0 to <1.5; Grade 3: ≥0.5 to <1.0; Grade 4: <0.5.
[c] Grade 1: decreased ≥10.5% to <24.5% and <LLN; Grade 2: decreased ≥24.5% to <49.5% and <LLN; Grade 3: decreased ≥49.5% to <74.5% and <LLN; Grade 4: decreased ≥74.5% and <LLN, or <$20x10^9$/L.

In a phase 2 study (PCYC-1102-CA), with a median treatment duration of 15.6 months, the following adverse reactions were reported at a greater incidence than in Study PCYC-1112-CA (≥5% difference; any grade): diarrhea (59%), bruising (51%), upper respiratory tract infection (39%), arthralgia (24%), constipation (22%), dizziness (20%), sinusitis (18%).

DRUG INTERACTIONS

Overview

Ibrutinib is metabolized primarily by cytochrome P450 enzyme 3A. Ibrutinib is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. IMBRUVICA™ should not be used concomitantly with strong inhibitors or inducers of CYP3A.

Drug-Drug Interactions

Agents that may increase ibrutinib plasma concentrations

Co-administration of ketoconazole, a strong CYP3A inhibitor, in healthy subjects increased exposure (C_{max} and AUC_{∞}) of ibrutinib by 29- and 26-fold, respectively. Co-administration of a mild or moderate CYP3A inhibitor with ibrutinib has not been studied clinically.

Concomitant use of strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, itraconazole, and cobicistat) and moderate inhibitors (e.g., voriconazole, erythromycin, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil) should be avoided.

If a strong CYP3A inhibitor must be used, withhold IMBRUVICA™ treatment temporarily for the duration of the inhibitor treatment. If a moderate CYP3A inhibitor must be used, reduce IMBRUVICA™ dose to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Patients should be monitored closely for toxicity. Follow dose modification guidelines as needed (see **DOSAGE AND ADMINISTRATION**).

Agents that may decrease ibrutinib plasma concentrations

Administration of IMBRUVICA™ with strong inducers of CYP3A (e.g., rifampin) decreases ibrutinib plasma exposures by approximately 10-fold and the dihydrodiol metabolite by 2.5-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction. IMBRUVICA™ can be administered concomitantly with mild inducers.

Drugs that may have their plasma concentrations altered by ibrutinib

Ibrutinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Ibrutinib may inhibit intestinal P-gp after a therapeutic dose and alter the absorption of co-dosed drugs that are P-gp substrates (e.g., aliskiren, digoxin, fexofenadine). There are no clinical data available.

In vitro studies have also demonstrated that ibrutinib inhibits the breast cancer resistance protein (BCRP). *In vivo* studies to confirm the transporter-based interaction have not been conducted. Ibrutinib may inhibit intestinal BCRP after a therapeutic dose and alter the absorption of co-dosed drugs that are BCRP substrates (e.g., methotrexate, topotecan, imatinib). Ibrutinib may also inhibit BCRP in the liver and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

To avoid a potential interaction in the GI tract, narrow therapeutic range BCRP and P-gp substrates should be taken at least 6 hours before or after IMBRUVICA™. Dose reduction of concomitant drugs that undergo BCRP-mediated hepatic efflux may be needed to avoid increased exposure and to reduce the risk of serious adverse reactions.

Anticoagulant and antiplatelet agents

Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA™. Use of IMBRUVICA™ in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding and should be used with caution (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Drug-Food Interactions

Grapefruit and Seville oranges must not be consumed during IMBRUVICA™ treatment as they contain moderate inhibitors of CYP3A (see **DOSAGE AND ADMINISTRATION**).

Supplements such as fish oil, flaxseed, and vitamin E preparations should be avoided as they may increase the risk of bleeding associated with IMBRUVICA™ (see **WARNINGS AND PRECAUTIONS, Hemorrhage**).

Administration with food increases exposure of ibrutinib and the dihydrodiol metabolite by approximately two-fold compared to administration after overnight fasting (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). IMBRUVICA™ can be taken with or without food.

Drug-Herb Interactions

Avoid concomitant use of St. John's Wort, as this herb is a strong inducer of CYP3A.

Drug-Lifestyle Interactions

Fatigue, dizziness and asthenia have been reported very commonly in patients taking IMBRUVICA™ and should be considered when assessing a patient's ability to drive or operate machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

IMBRUVICA™ should be administered orally, with or without food, with a glass of water once daily, at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA™ must not be taken with grapefruit juice. Treatment with IMBRUVICA™ should continue until disease progression or until no longer tolerated by the patient.

Upon initiation of treatment with IMBRUVICA™, a reversible increase in lymphocyte counts, often associated with reduction of lymphadenopathy, has been observed in most patients with CLL treated. This observed lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings (see **ACTION AND CLINICAL PHARMACOLOGY**).

Recommended Dose and Dosage Adjustment

The recommended dose of IMBRUVICA™ for CLL is 420 mg (three 140 mg capsules) once daily.

IMBRUVICA™ therapy should be withheld for any new onset or worsening Grade ≥3 non-hematological, Grade ≥3 neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), IMBRUVICA™ therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue IMBRUVICA™.

Recommended dose modifications for these toxicities are described below:

Toxicity occurrence	**CLL dose modification after recovery**
First	restart at 420 mg daily
Second	restart at 280 mg daily
Third	restart at 140 mg daily
Fourth	discontinue IMBRUVICA™

Patients with Hepatic Impairment

IMBRUVICA™ should not be used in patients with moderate (Child-Pugh class B) or severe hepatic impairment (Child-Pugh class C) (see **WARNINGS AND PRECAUTIONS, Special Populations**). If the benefit is considered to outweigh the risk in a patient with mild hepatic impairment (Child Pugh class A), a dose reduction to 140 mg should be considered. Monitor patients for signs of toxicity.

Concomitant use of CYP3A Inhibitors

Concomitant use of moderate and strong CYP3A inhibitors increases the exposure of ibrutinib (see **DRUG INTERACTIONS**). If a strong CYP3A inhibitor must be used, withhold treatment with IMBRUVICA™ temporarily for the duration of the inhibitor treatment. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA™ dose to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Patients should be monitored closely for toxicity. Follow dose modification guidelines as needed.

Missed Dose

If a dose of IMBRUVICA™ is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

OVERDOSAGE

There are limited data on the effects of IMBRUVICA™ overdose. No Maximum Tolerated Dose was reached in the Phase 1 study in which a small number of patients received up to 12.5 mg/kg/day. There is no specific antidote for IMBRUVICA™. Patients who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibrutinib is a small-molecule, targeted inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is a signaling molecule of the B-cell antigen receptor (BCR) pathway. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies including CLL. In addition to its roles in antigen mediated BCR signaling, BTK is involved in signaling of chemokine receptors such as CXCR4 and CXCR5 that play roles in B-cell trafficking and tissue homing. Nonclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival as well as cell migration and substrate adhesion.

Pharmacodynamics

Lymphocytosis

Upon initiation of treatment with IMBRUVICA™, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (70%) with CLL. This observed lymphocytosis may be a pharmacodynamic effect of the inhibition of BTK-mediated cellular homing and adhesion, and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis typically occurs during the first few weeks of IMBRUVICA™ therapy (median time 1.1 weeks) and typically resolves within a median 14.1 weeks in patients with CLL.

A large increase in the number of circulating lymphocytes (e.g., to above 400,000/mcL) has been observed in some patients and may confer increased risk of leukostasis.

Electrocardiography

In an uncontrolled Phase 2 study (PCYC-1102-CA), IMBRUVICA™ was administered to subjects with CLL at daily doses of 420 mg or 840 mg. Central, time-matched ECG data were collected on days 1, 8, 15, 22 and 28; however, triplicate on-treatment ECGs were not collected, and baseline ECGs were collected over a two-week period. No evidence of QT/QTc interval prolongation was observed. A QTcF interval shortening by an average of 8.9 ms relative to baseline was observed, with no evidence of dose dependency.

Pharmacokinetics

Absorption

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. The bioavailability of ibrutinib has not been studied and is estimated to be low due to high first-pass metabolism. Ibrutinib exposure increases with doses up to 840 mg. The mean (SD) steady state $AUC_{0\text{-}24h}$ observed in patients at 420 mg is 732 (521) ng.h/mL with C_{max} 137 (118) ng/mL. High intersubject variability of exposures was observed in patients.

Administration with food increases the exposures of ibrutinib and the dihydrodiol metabolite by approximately two-fold compared to administration after overnight fasting. A delay in T_{max} (from ~2 to 4 hours) was also observed with food.

Distribution

Binding of ibrutinib to human plasma proteins *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The apparent volume of distribution at steady state ($V_{d,ss}/F$) is approximately 10,000 L. Binding of the dihydrodiol metabolite to human plasma protein *in vitro* is 91% at 475 ng/mL.

The proportion of unbound ibrutinib is inversely related to the plasma levels of α1-acid glycoprotein and albumin in humans. Approximately 12% C_{max} and 51% $AUC_{0\text{-}72h}$ of total radioactivity were accounted for by covalent binding in the plasma of healthy male volunteers administered a single dose of 140 mg ibrutinib admixed with ^{14}C-ibrutinib. *In vitro*, ibrutinib binds both reversibly and covalently to human serum albumin and, to a lesser extent, to α1-acid glycoprotein.

Metabolism

Ibrutinib is extensively metabolized, primarily by cytochrome P450, CYP3A, to produce a prominent dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Systemic steady-state exposure to the dihydrodiol metabolite is 2.5-fold that of the parent drug in patients administered 420 mg daily dose. Other main circulating metabolites include M25 (oxidative opening of the piperidine with further oxidation to a carboxylic acid), M34 (oxidative opening of the piperidine with further reduction to a primary alcohol) and M21 (sulphate conjugate of hydroxylated phenyl moiety). M25 and M34 have negligible activity towards BTK and activity of M21 has not been studied. Steady-state exposure of these metabolites is not known.

In vitro studies suggest that CYP2D6 involvement in ibrutinib oxidative metabolism is minor. *In vitro* enzyme kinetic studies demonstrated that the rate of metabolism of ibrutinib to its dihydrodiol metabolite by human recombinant CYP2D6 was lower with the poor metabolizer phenotype compared to that of wildtype. As part of the human mass balance study, two subjects genotyped as poor metabolizers for CYP2D6, showed a similar pharmacokinetic profile as four extensive metabolizers.

Elimination

Apparent clearance (CL/F) of ibrutinib is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. The half-life of the dihydrodiol metabolite is 6 to 11 hours. Accumulation of less than two-fold of both parent compound and the dihydrodiol metabolite following daily dose regimen was observed.

After a single oral administration of 140 mg ibrutinib admixed with [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Drug-drug interactions

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA™ was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA™ was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 to 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC_{last} 29-fold and 24-fold, respectively. The corresponding decrease in dose-normalized C_{max} and AUC_{last} of the dihydrodiol metabolite was 2.6-fold and 1.2-fold, respectively. Drug-drug interaction studies of ibrutinib with moderate or mild inhibitors of CYP3A have not been conducted. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition.

In a sequential design trial of 18 healthy volunteers, a single dose of 560 mg of IMBRUVICA™ was administered alone on Day 1 and on Day 11 in combination with 600 mg of rifampin (given daily on Days 4 to 13). Rifampin (a strong CYP3A inducer) decreased ibrutinib C_{max} and AUC_{last} 13-and 10-fold, respectively. The corresponding decrease in C_{max} and AUC_{last} of the dihydrodiol metabolite was 1.4- and 2.5-fold, respectively. Drug-drug interaction studies of ibrutinib with moderate or mild inducers of CYP3A have not been conducted. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

Ibrutinib did not significantly affect the *in vitro* plasma protein binding of warfarin (bound predominantly to albumin).

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor

toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes *in vitro*. Inhibition or induction of CYP450 enzymes by ibrutinib and the dihydrodiol metabolite is unlikely to lead to a clinically relevant drug interaction with drugs that are CYP450 substrates.

Special Populations and Conditions

Pediatrics (<18 years of age)

No pharmacokinetic studies were performed with IMBRUVICA™ in patients under 18 years of age.

Geriatrics (≥65 years of age)

Pharmacokinetic data in patients administered 420 mg daily dose showed higher systemic exposures of ibrutinib (25% higher AUC and 50% higher C_{max}) and the dihydrodiol metabolite (48% higher AUC and 56% higher C_{max}) at steady state in patients ≥65 years of age when compared with those <65 years.

Gender

Pharmacokinetic data in patients administered 420 mg daily dose showed approximately 34% higher steady state exposure of the dihydrodiol metabolite in female patients when compared with males whereas ibrutinib exposures were comparable. Population pharmacokinetics data indicated that gender does not significantly affect ibrutinib clearance from the circulation.

Hepatic Impairment

Ibrutinib is metabolized in the liver. In a dedicated hepatic impairment trial in non-cancer patients administered a single dose of 140 mg of IMBRUVICA™, preliminary data showed up to 9- and 13-fold increase in exposure of total ibrutinib and unbound ibrutinib, respectively, in subjects with hepatic impairment.

Renal Impairment

No specific clinical studies have been conducted in subjects with impaired renal function. Ibrutinib has minimal renal clearance; urinary excretion of metabolites is <10% of the dose. There are no data in patients with severe renal impairment or patients on dialysis.

STORAGE AND STABILITY

Store at room temperature between 15°C-30°C. Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

IMBRUVICA™ (ibrutinib) 140 mg capsules are white, marked with “ibr 140 mg” in black ink.

Composition

IMBRUVICA™ (ibrutinib) for oral administration is available as 140 mg strength hard gelatin capsules. Each capsule contains 140 mg of ibrutinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The white capsule shell contains gelatin and titanium dioxide (E171). Capsules are printed with ink containing iron oxide black (E172) and shellac.

Packaging

IMBRUVICA™ capsules are packaged in high-density polyethylene (HDPE) bottles of 90 or 120 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

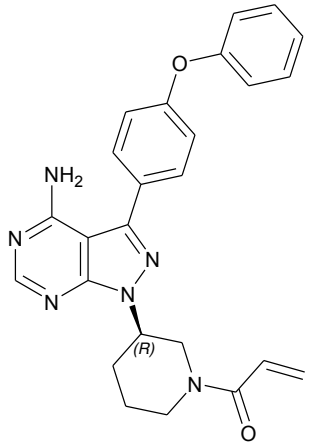
Drug Substance

Common name: ibrutinib

Chemical name: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one

Molecular formula and molecular mass: $C_{25}H_{24}N_6O_2$ and 440.50 g/mol

Structural formula:



Physicochemical properties:

Appearance: Ibrutinib is a crystalline white to off-white solid.

Solubility: Ibrutinib is practically insoluble in water over a wide pH range (pH 3 to 8).

Dissociation Constant: The drug substance has one ionizable group, the protonated pyrimidine moiety, with a pKa of 3.74.

CLINICAL TRIALS

The safety and efficacy of IMBRUVICA™ in patients with CLL who have received at least one prior therapy were demonstrated in one randomized, controlled trial (PCYC-1112-CA), and one uncontrolled trial (PCYC-1102-CA).

PCYC-1112-CA

A randomized, multi-center, open-label Phase 3 study of IMBRUVICA™ versus ofatumumab was conducted in patients with previously treated CLL, including 18 patients with clinical presentation of SLL. Patients were eligible for the study if they failed to respond to prior therapy,

relapsed following a response to prior therapy, or otherwise met the 2008 International Workshop on CLL (IWCLL) criteria for active disease requiring treatment following at least one prior therapy, and were not appropriate for treatment or retreatment with purine analog. Patients (n=391) were randomized 1:1 to receive either IMBRUVICA™ 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2000 mg). Fifty-seven patients randomized to ofatumumab crossed over following progression to receive IMBRUVICA™. The median age was 67 years (range, 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range, 1 to 13 treatments). At baseline, 58% of patients had at least one tumour ≥5 cm. Thirty-two percent of patients had 17p deletion and 31% had 11q deletion.

At a median duration of follow-up of 9.6 months in the ibrutinib arm and 9.2 months in the ofatumumab arm, progression-free survival (PFS) as assessed by independent review committee (IRC) according to 2008 IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA™ arm. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA™ arm. Efficacy results are shown in Table 3 and the Kaplan-Meier curves for PFS and OS are shown in Figures 2 and 3, respectively.

Table 3: Efficacy results in patients with Chronic Lymphocytic Leukemia (Study PCYC-1112-CA)

Endpoint	**IMBRUVICA™ N=195**	**Ofatumumab N=196**
Median Progression Free Survival	Not reached	8.1 months
	HR=0.22 [95% CI: 0.15; 0.32]	
Overall Survival[a]	HR=0.43 [95% CI: 0.24; 0.79][b] HR=0.39 [95% CI: 0.22 0.70][c]	
Overall Response Rate[d,e]	42.6%	4.1%
Overall Response Rate with PRL[d]	62.6%	4.1%

[a] Median OS not reached for both arms.
[b] Patients randomized to ofatumumab who progressed were censored when starting ibrutinib if applicable.
[c] Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of IMBRUVICA™.
[d] Per IRC. Repeat CT scans required to confirm response.
[e] All PRs achieved; none of the patients achieved a CR. $p<0.0001$ for ORR.

The efficacy was similar across all of the subgroups examined, including in patients with and without 17p deletion (a pre-specified stratification factor), patients with and without deletion 11q, patients refractory and not refractory to prior purine analog treatment, patients with and without advanced disease (Rai stage 0-II and stage III-IV), and patients with and without bulky lymphadenopathy (<5 cm and ≥5 cm) (Figure 1).

Figure 1: Subgroup Analysis of Progression-Free Survival by IRC (Study PCYC-1112; 420 mg)

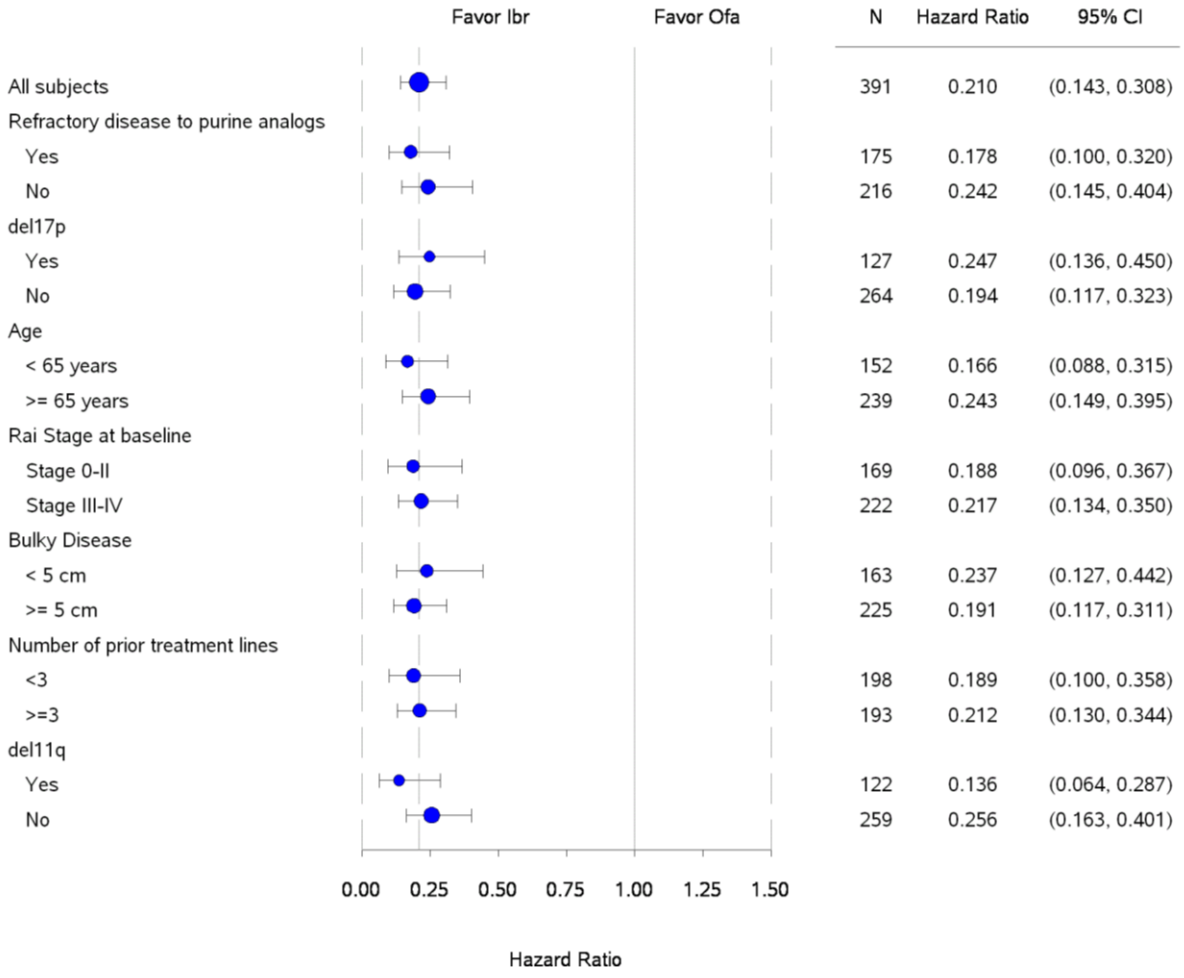


Figure 2: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

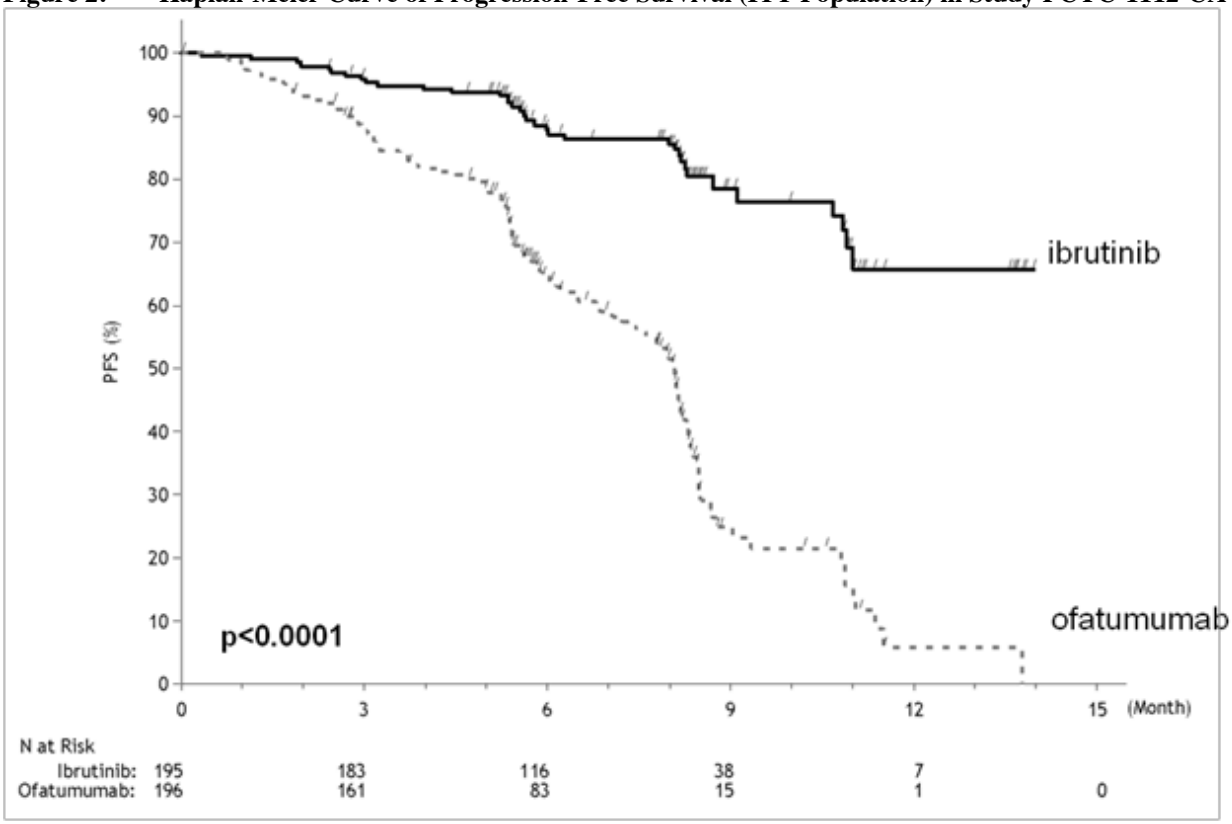
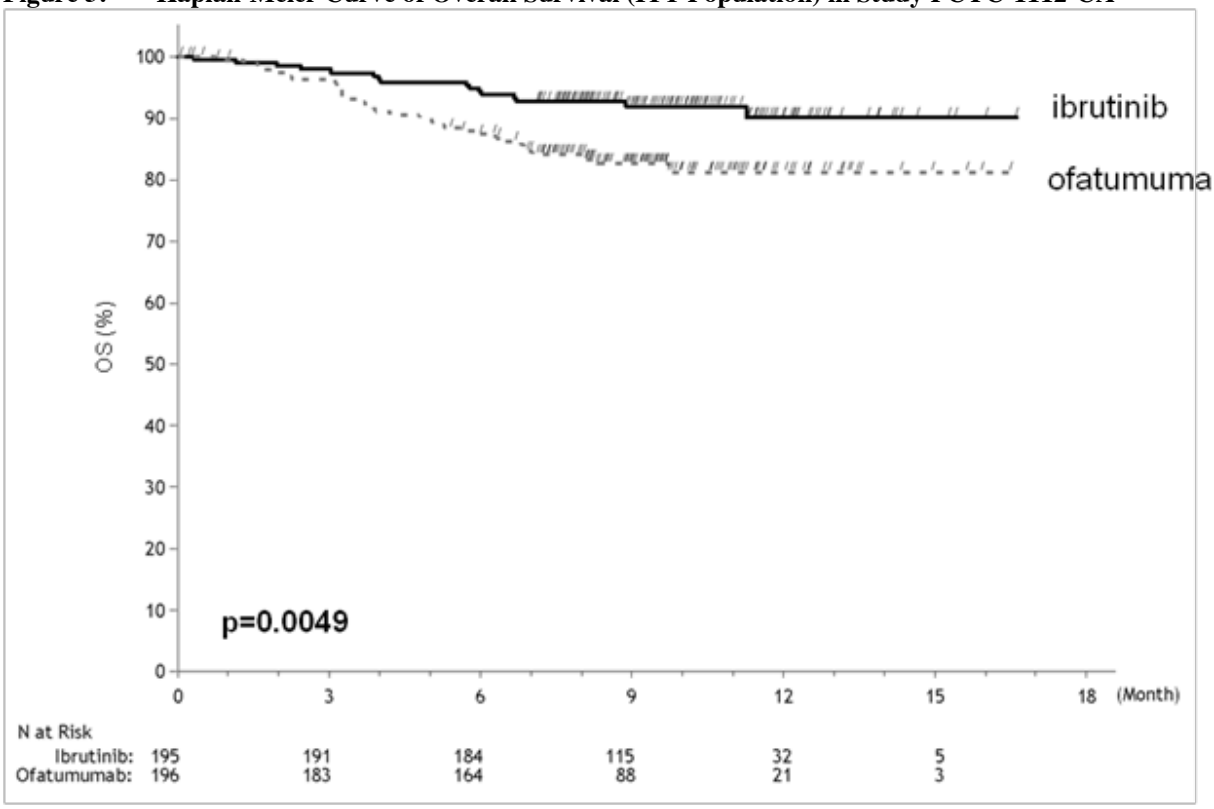


Figure 3: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



CLL with 17p deletion

Study PCYC-1112-CA included 127 patients with CLL with 17p deletion. The median age was 67 years (range, 30 to 84 years), 62% were male, and 88% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. PFS and ORR were assessed by IRC. Efficacy results for CLL with 17p deletion are shown in Table 4.

Table 4: Efficacy results in patients with CLL with 17p deletion (Study PCYC-1112-CA)

Endpoint	IMBRUVICA™ N=63	Ofatumumab N=64
Median Progression Free Survival	Not reached	5.8 months
	HR=0.25 [95% CI: 0.14; 0.45]	
Overall Response Rate[a]	47.6%	4.7%
Overall Response Rate with PRL	66.7%	4.7%

[a] IRC evaluated. All partial responses achieved; none of the patients achieved a complete response. HR=hazard ratio.

PCYC-1102-CA

An open-label, multi-center study (PCYC-1102-CA) was conducted in 51 patients with a confirmed diagnosis of relapsed or refractory CLL who have failed at least 1 prior therapy, including 3 patients with clinical presentation of SLL. Patients received IMBRUVICA™ 420 mg once daily until disease progression or unacceptable toxicity. The median age was 68 (range, 37 to 82 years), median time since diagnosis was 80 months, and median number of prior treatments was 4 (range, 1 to 12 treatments). At baseline, 39.2% of patients had Rai Stage IV, 45.1% had bulky disease (at least one tumour ≥5 cm), 35.3% had 17p deletion, and 31.4% had 11q deletion.

ORR was investigator-assessed according to the 2008 IWCLL criteria. At a median duration of follow up of 16.4 months, ORR (CR+PR) was 78.4% (95% CI: 64.7%; 88.7%), ORR including Partial Response with Lymphocytosis was 92.2%, median duration of response was not reached, and median (range) time to initial response was 1.8 months (1.4 to 12.2 months).

DETAILED PHARMACOLOGY

Pharmacodynamics

The effects of ibrutinib and the dihydrodiol metabolite on hERG channel-mediated ion current were evaluated in voltage-clamped HEK293 cells that stably express hERG potassium channels. The IC_{50} for inhibitory effect of ibrutinib on hERG channel current was 970 nM (427 ng/mL). The IC_{50} for inhibitory effect of the dihydrodiol metabolite on hERG channel current was 9600 nM (4555 ng/mL).

The acute effects of ibrutinib treatment on cardiovascular function were also assessed in dogs up to doses of 150 mg/kg. Lowered heart rate and increased blood pressure were observed at doses ≥24 mg/kg (≥7.2 times human exposure based on C_{max}). There was no treatment-related prolongation of QT_c intervals observed at any dose level. Shortening of the QTc interval was observed at a dose of 150 mg/kg (≥5.6 times human exposure based on C_{max}).

There were no ibrutinib-related acute effects on CNS or respiratory function in rats at doses up to 150 mg/kg (approximately 22 times human exposure based on C_{max}).

TOXICOLOGY

Carcinogenicity and Mutagenicity

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not genotoxic *in vitro* in bacterial reverse mutation (Ames) and chromosomal aberrations assays. Ibrutinib was also non-clastogenic *in vivo* in the mouse bone marrow erythrocyte micronucleus assay.

Chronic Toxicity

In rats and dogs, lymphoid organs and the gastrointestinal tract were identified as target organs/tissues of toxicity. Additional histopathological changes were noted in the pancreas and bone in rats, but were not observed in dogs.

The following adverse effects were seen in studies up to 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft feces/diarrhea and/or inflammation) in rats at human equivalent doses (HEDs) ≥16 mg/kg/day and in dogs at HEDs ≥32 mg/kg/day (≥4 times human clinical exposure based on AUC). Effects on lymphoid tissue (lymphoid depletion) were also induced at HEDs ≥28 mg/kg/day in rats and ≥32 mg/kg/day in dogs (≥4 times human clinical exposure based on AUC). In rats, moderate pancreatic acinar cell atrophy was observed after 13 weeks of administration at HEDs ≥16 mg/kg/day (≥8 times human clinical exposure based on AUC). Mildly decreased trabecular and cortical bone was seen in female rats administered HEDs ≥16 mg/kg/day for 13 weeks (≥8 times human clinical exposure based on AUC). All notable findings in rats and dogs fully or partially reversed following recovery periods of 6 to 13 weeks.

Fertility

Fertility studies with ibrutinib have not been conducted in animals.

Reproductive and Developmental Toxicity

In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

Ibrutinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 10, 40 and 80 mg/kg/day. At a dose of 80 mg/kg/day (approximately 18 times the AUC of ibrutinib and 9.1 times the AUC of the dihydrodiol metabolite compared to patients at the dose of 420 mg daily), ibrutinib was associated with increased post-implantation loss and increased visceral malformations (heart and major vessels). At a dose of ≥40 mg/kg/day (≥ approximately

7.3 times the AUC of ibrutinib and 3.9 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 420 mg daily), ibrutinib was associated with decreased fetal weights.

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PART III: CONSUMER INFORMATION

PrIMBRUVICA™
ibrutinib capsules

This leaflet is a summary and will not tell you everything about IMBRUVICA™. Contact your doctor or pharmacist if you have any questions about the drug. This leaflet is Part III of a three-part "Product Monograph" published when IMBRUVICA™ was approved for sale in Canada and is designed specifically for Consumers.

ABOUT THIS MEDICATION

What the medication is used for:
IMBRUVICA™ is used to treat people with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy, including those with a deletion of the "TP53" gene (17p deletion), or for the initial treatment of people with CLL with a deletion of the "TP53" gene (17p deletion).

CLL is a cancer of the immune system that affects a certain type of white blood cell called B-lymphocytes (also referred to as B cells).

What it does:
IMBRUVICA™ blocks a specific protein in the body that helps cancer cells live and grow. This protein is called "Bruton's Tyrosine Kinase." By blocking this protein, IMBRUVICA™ may help kill and reduce the number of cancer cells and slow the spread of the cancer.

When it should not be used:
Do not take IMBRUVICA™ if you are allergic to ibrutinib or any of the other ingredients in this medicine or components of the container. If you are not sure about this, talk to your doctor before taking IMBRUVICA™.

What the medicinal ingredient is:
The medicinal ingredient in IMBRUVICA™ is ibrutinib.

What the nonmedicinal ingredients are:
The nonmedicinal ingredients in IMBRUVICA™ are: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate.

What dosage forms it comes in:
IMBRUVICA™ is available as a capsule that contains 140 mg of ibrutinib.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Major bleeding events have been reported (see below)
- Should not be used in patients with moderate or severe liver impairment (see below)
- Should not be used with certain medications that can increase the blood level of IMBRUVICA™ (see below)

BEFORE you use IMBRUVICA™ talk to your doctor or pharmacist if you:
- have ever had unusual bleeding or bruising or are on any medicines that increase your risk of bleeding such as aspirin, anti-inflammatories (e.g., ibuprofen, naproxen, and others), warfarin, heparin, other medications to prevent or treat blood clots (e.g., dabigatran, rivaroxaban, apixaban), or any supplements that increase your risk of bleeding such as fish oil, flaxseed, or vitamin E. You should not take warfarin (COUMADIN®).
- have or have had an irregular heart beat (atrial fibrillation) or severe heart failure, which makes you short of breath and may lead to swollen legs.
- have liver or kidney problems. You should not take this drug if you have certain liver problems.
- are planning to have any medical, surgical or dental procedure. Your doctor may ask you to stop taking IMBRUVICA™ for a short time.
- have any infection.
- are pregnant or plan to become pregnant. IMBRUVICA™ can harm your unborn baby. Do not get pregnant while taking IMBRUVICA™. You must use two forms of effective birth control methods together during treatment with IMBRUVICA™ and for at least 3 months after the last dose of IMBRUVICA™.
- are planing to breastfeed. Do not breastfeed while you are taking IMBRUVICA™.
- plan to father a child. Do not father a child while taking IMBRUVICA™ and for 3 months after stopping treatment. Use condoms and do not donate sperm during treatment and for 3 months after your treatment has finished.

Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with IMBRUVICA™.

IMBRUVICA™ is not recommended for use in patients under 18 years of age.

IMBRUVICA™ may affect your ability to drive and use machines. DO NOT drive or operate machines while taking IMBRUVICA™.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the prescription and over-the-counter medications you take, including vitamins and herbal supplements. Taking IMBRUVICA™ with certain other medicines may affect how IMBRUVICA™ and other medicines work and can cause side effects. The following is not a complete list of medications with which IMBRUVICA™ may interact.

Tell your doctor if you take any of these medications that can increase the amount of IMBRUVICA™ in your blood:

- Antibiotics (such as clarithromycin, ciprofloxacin, erythromycin).
- Antifungals (such as ketoconazole, itraconazole, fluconazole, voriconazole).
- Antivirals for HIV infection (such as indinavir, nelfinavir, ritonavir, saquinavir, atazanavir, darunavir/ritonavir, cobicistat, fosamprenavir).
- aprepitant – used to prevent nausea and vomiting.
- crizotinib – used for lung cancer.
- diltiazem – used for high blood pressure and chest pain.
- verapamil – used for high blood pressure, chest pain, irregular heart beat and other heart problems.
- imatinib – used for several types of blood cancer.

Tell your doctor if you take any of these medications that can decrease the amount of IMBRUVICA™ in your blood:

- Anticonvulsants (such as carbamazepine and phenytoin).
- Antibiotics (such as rifampin).
- St. John's Wort – a herbal medicine used for depression.

You must tell your doctor if you take other medicines that increase your risk of bleeding, such as aspirin, blood thinners, or anti-inflammatories (such as ibuprofen, naproxen) or supplements such as fish oil, flaxseed, or vitamin E.

While you are taking IMBRUVICA™, you should not drink grapefruit juice, eat grapefruit or Seville oranges, or take supplements containing grapefruit extract. These products may increase the amount of IMBRUVICA™ in your blood.

PROPER USE OF THIS MEDICATION

Usual dose:
Take IMBRUVICA™ as prescribed by your doctor.

The recommended dose is 420 mg (3 capsules) once a day, taken by mouth. Do not change your dose or stop taking IMBRUVICA™ unless your doctor tells you to.

Swallow IMBRUVICA™ capsules whole, with a glass of water. Do not take IMBRUVICA™ with grapefruit juice or Seville oranges; this includes eating them, drinking the juice, or taking supplements that might contain them. Do not open, break or chew IMBRUVICA™ capsules.

Take IMBRUVICA™ at about the same time each day.

Drink plenty of fluids to stay hydrated while taking IMBRUVICA™. This will help your kidneys continue to function properly.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose of IMBRUVICA™ take it as soon as you remember on the same day. Take your next dose of IMBRUVICA™ at your regular time on the next day. Do not take extra capsules of IMBRUVICA™ to make up for a missed dose. Call your doctor or pharmacist if you are not sure of what to do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, IMBRUVICA™ can cause side effects.

The following side effects may happen with IMBRUVICA™:

Very common (occurring in 10 or more patients per 100):

- Lymphocytosis: An increase in the number of white blood cells, specifically lymphocytes. This increase in white blood cells is expected in the first few weeks of treatment and may last for 3 or more months. Your doctor will monitor your blood counts. Talk to your doctor about what your blood test results mean.
- Diarrhea: You may experience an increase in frequency of loose or watery stools, sometimes requiring the use of antidiarrheal medications or fluid and electrolyte replacement to prevent dehydration. Contact your doctor if your diarrhea persists.
- Viral, bacterial, or fungal infections: Infections can be serious and may lead to death. Contact your doctor if you have fever, chills, or any other signs or symptoms of a possible infection.
- Bleeding, bruising, small red or purple spots caused by bleeding under the skin: You may experience bruising or nosebleeds during treatment with IMBRUVICA™. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur. If you take other medicines that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), or medicines used to prevent or treat blood clots or strokes, IMBRUVICA™ may increase this risk. Do not take supplements that increase your risk of bleeding, such as fish oil, flaxseed, or vitamin E. Call your doctor if you have signs or symptoms of serious bleeding, such as blood in your stools or urine, bleeding that lasts for a long time or that you cannot control, coughing up blood or blood clots, increased bruising,

feel dizzy or weak, confusion, change in your speech, or a headache that lasts a long time.
- Decrease in blood cell counts: Use of IMBRUVICA™ may cause you to have a low number of red blood cells (anemia), white blood cells or platelets (cells that help blood to clot). Your doctor should check your blood counts regularly.
- Muscle aches, joint aches
- Headache, dizziness, weakness
- Rash

Common (occurring in 1 to 9 patients per 100):
- Heart problems: Irregular heart beat (atrial fibrillation). Tell your doctor if you develop any heart problems.
- New cancers have happened in people taking IMBRUVICA™, including skin cancer and other cancers.

Uncommon (occurring in 1 to 9 patients per 1000):
- Unusual levels of chemical in the blood caused by the fast breakdown of cancer cells (tumour lysis syndrome) have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or healthcare provider may do blood tests to check for tumour lysis syndrome.

Allergic reaction: Stop using IMBRUVICA™ and get emergency medical help if you have any of these signs of an allergic reaction: hives, difficulty breathing, or swelling of your face, lips, tongue, or throat.

This is not a complete list of side effects and others may occur. Tell your doctor if you have any side effect that bothers you or does not go away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist: Only if severe	Talk with your doctor or pharmacist: In all cases	Stop taking drug and call your doctor or pharmacist
Very common (occurring in 10 or more patients per 100)			
Low red blood cells, low white blood cells, low platelets		✓	
Diarrhea, nausea, sore mouth, constipation, vomiting	✓		
Fever		✓	
Common cold, pneumonia, sinus infection		✓	
Muscle aches, joint aches	✓		
Headache, dizziness	✓		
Rash	✓		
Bruising, small red or purple spots caused by bleeding under the skin	✓		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist: Only if severe	Talk with your doctor or pharmacist: In all cases	Stop taking drug and call your doctor or pharmacist
Common (occurring in 1 to 9 patients per 100)			
Increased white blood cells		✓	
Fever with low white cells		✓	
Irregular heart rhythm		✓	
Blurred vision	✓		
Urinary tract infection, skin infection, infection of the blood		✓	
Nose bleeds		✓	
Bleeding in the brain			✓
Uncommon (occurring in 1 to 9 patients per 1000			
Unusual levels of chemical in the blood (tumour lysis syndrome)			✓

This is not a complete list of side effects. For any unexpected effects while taking IMBRUVICA™*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store IMBRUVICA™ at room temperature between 15ºC and 30ºC.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada, Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.janssen.ca
or by contacting the sponsor, Janssen Inc. at:
1-800-567-3331 or 1-800-387-8781

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