**IMBRUVICA**®
Ibrutinib capsules

**DOSAGE FORMS AND STRENGTHS**
**Capsules**
140mg capsules
IMBRUVICA capsules contain 140 mg of ibrutinib.
White opaque, size 0, hard gelatin capsule marked with "ibr 140 mg" in black ink.

For excipients, see *List of Excipients*.

**CLINICAL INFORMATION**
**INDICATIONS**
**Mantle cell lymphoma (MCL)**
Indicated for the treatment of adult patients with relapsed or refractory MCL.
**Chronic lymphocytic leukemia (CLL)**
IMBRUVICA as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) (see *Pharmacodynamic properties*).
IMBRUVICA as a single agent is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
**Chronic lymphocytic leukemia with deletion 17p**
Indicated for the treatment of patients with CLL with deletion 17p.

**DOSAGE AND ADMINISTRATION**
**Dosage**
IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water. Do not open, break, or chew the capsules. IMBRUVICA must not be taken with grapefruit juice. IMBRUVICA should continue until disease progression or no longer tolerated by the patient.

***Mantle cell lymphoma***
The recommended dose of IMBRUVICA for MCL is 560 mg once daily until disease progression or no longer tolerated by the patient.

***Chronic lymphocytic leukemia (CLL)***
The recommended dose for the treatment of CLL is 420mg (three capsules) once daily.
Treatment should continue until disease progression or no longer tolerated by the patient.

***Dose modification guidelines***
Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see *Interactions*).
IMBRUVICA therapy should be withheld for any new onset or worsening Grade ≥ 3 non-hematological toxicities, Grade 3 or greater 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 are described below:

| Toxicity occurrence | MCL dose modification after recovery | CLL dose modification after recovery |
|---|---|---|
| First | restart at 560 mg daily | restart at 420 mg daily |
| Second | restart at 420 mg daily | restart at 280 mg daily |
| Third | restart at 280 mg daily | restart 140 mg daily |
| Fourth | discontinue IMBRUVICA | |

***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.

***Special populations***
***Pediatrics (18 years of age and younger)***
The safety and efficacy of IMBRUVICA in children have not yet been evaluated.

***Renal impairment***
Ibrutinib has minimal renal clearance. No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). 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 *Pharmacokinetic Properties*).

***Hepatic impairment***
Ibrutinib is metabolized in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see *Pharmacokinetic Properties*). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

**CONTRAINDICATIONS**
IMBRUVICA is contraindicated in patients who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to ibrutinib or to the excipients in its formulation.
Use of preparations containing St. John's Wort is contraindicated in patients treated with Imbruvica.

**WARNINGS AND PRECAUTIONS**
**Bleeding-related events**
There have been reports of bleeding events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.
In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed (see *Pharmacodynamic Properties*). Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.
Supplements such as fish oil and vitamin E preparations should be avoided.
IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

**Leukostasis**
There were isolated cases of leukostasis reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (> 400000/mcL) may confer increased risk. Consider temporarily with holding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

**Infections**
Infections (including sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in patients treated with IMBRUVICA. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy.
Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

**Cytopenias**
Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

**Interstitial Lung Disease (ILD)**
Cases of ILD have been reported in patients treated with IMBRUVICA. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt IMBRUVICA and manage ILD appropriately. If symptoms persist, consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

**Cardiac arrhythmia**
Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia including some fatal events, have been reported in patients treated with IMBRUVICA. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms or new onset of dyspnea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.
In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, IMBRUVICA should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.
In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

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

**Non-melanoma skin cancer**
Non-melanoma skin cancers were reported more frequently in patients treated with IMBRUVICA than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

**Hypertension**
Hypertension has occurred in patients treated with IMBRUVICA. Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

**Viral reactivation**
Cases of hepatitis B reactivation have been reported in patients receiving IMBRUVICA. Hepatitis B virus (HBV) status should be established before initiating treatment with IMBRUVICA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

**Drug-drug interactions**
Co-administration of strong or moderate CYP3A4 inhibitors with IMBRUVICA may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of IMBRUVICA with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy.

**Women of Childbearing potential**
Women of childbearing potential must use a highly effective method of contraception while taking Imbruvica.

**INTERACTIONS**
Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4 (CYP3A4).

**Agents that may increase ibrutinib plasma concentrations**
Concomitant use of IMBRUVICA and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A should be avoided.

***Strong CYP3A inhibitors***
Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure ($C_{max}$ and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in patients with B-cell malignancies, co-administration of voriconazole increased $C_{max}$ and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in the table below. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see recommended dose modifications in the table below.

***Moderate and mild CYP3A inhibitors***
In patients with B-cell malignancies, co-administration of CYP3A inhibitor erythromycin increased $C_{max}$ and AUC by 3.4-fold and 3.0-fold, respectively. If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce IMBRUVICA dose as per recommended dose modifications in the table below.

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during IMBRUVICA treatment as these contain moderate inhibitors of CYP3A (see *Dosage and Administration* and *Pharmacokinetic Properties*).

***Recommended dose modifications are described below:***

| Patient Population | Co-administered Drug | Recommended IMBRUVICA Dose for the Duration of the Inhibitor Use[a] |
|---|---|---|
| B-Cell Malignancies | • Mild CYP3A inhibitors | 420 mg or 560 mg once daily per indication. No dose adjustment required. |
| | • Moderate CYP3A inhibitors | 280 mg once daily. |
| | • Voriconazole<br>• Posaconazole at doses less than or equal to suspension 200 mg BID | 140 mg once daily. |
| | • Other strong CYP3A inhibitors<br>• Posaconazole at higher doses[b] | Avoid concomitant use and consider alternative with less CYP3A inhibitory potential.<br>If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.<br>If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce IMBRUVICA dose to 140 mg once daily for the duration of the inhibitor use. |

[a] Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see *Dosage and Administration*).
[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA (see *Dosage and Administration*).

**Agents that may decrease ibrutinib plasma concentrations**
Administration of IMBRUVICA with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

**Drugs that may have their plasma concentrations altered by ibrutinib**
*In vitro* studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. 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*. Therefore, it is unlikely that IMBRUVICA has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

*In vitro* studies indicated that ibrutinib is not a substrate of P-gp nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after IMBRUVICA. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

**Pregnancy, Breast-feeding and Fertility**
**Pregnancy**
There are no adequate and well-controlled studies of IMBRUVICA in pregnant women. Based on findings in animals, 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. Those using hormonal methods of birth control must add a barrier method. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 1 month after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown.
Men should be advised not to father a child or donate sperm while receiving IMBRUVICA, and for 3 months following completion of treatment (see *Non-Clinical Information - Fertility*).
Ibrutinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 10, 40, and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day (approximately 14 times the AUC of ibrutinib and 9.5 times the AUC of the dihydrodiol metabolite compared to patients at the dose of 560 mg daily) was associated with increased post-implantation loss and increased visceral malformations (heart and major vessels). Ibrutinib at a dose of ≥ 40 mg/kg/day (≥ approximately 5.6 times the AUC of ibrutinib and 4.0 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 560 mg daily) was associated with decreased fetal weights.
Ibrutinib was also administered orally to pregnant rabbits during the period of organogenesis at oral doses of 5, 15, and 45 mg/kg/day. Ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL receiving ibrutinib dose 420 mg per day).

**Breast-feeding**
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 in nursing infants from IMBRUVICA, breast-feeding should be discontinued during IMBRUVICA treatment.

**Effects on Ability to Drive and Use Machines**
Fatigue, dizziness, and asthenia have been reported in some patients taking IMBRUVICA and should be considered when assessing a patient's ability to drive or operate machines.

**ADVERSE REACTIONS**
Throughout this section, adverse reactions (AR) are presented. Adverse reactions are adverse events that have been considered to be reasonably causally 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. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Non-melanoma skin cancer**
Based on an integrated analysis of the randomized, controlled phase 3 studies, the incidence of non-melanoma skin cancer was 6% in IMBRUVICA-treated patients and 3% in comparator-treated patients.

**Leukostasis**
Isolated cases of leukostasis have been observed (see *Warnings and Precautions*).

**Elderly**
Of the 1200 patients treated with IMBRUVICA, 64% were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (≥5%) among elderly patients treated with IMBRUVICA (12% of patients ≥ 65 years of age versus 7% of patients <65 years of age).

**Mantle cell lymphoma**
The data described below reflect exposure to IMBRUVICA in a phase 2 clinical study (PCYC-1104-CA) and a randomized phase 3 study (MCL3001) in patients with MCL (n=250).

The most commonly occurring adverse reactions for MCL (≥ 20%) were diarrhea, hemorrhage (e.g., bruising), fatigue, musculoskeletal pain, nausea, upper respiratory tract infection, cough, and rash.

The most common Grade 3/4 adverse reactions (≥ 5%) were: neutropenia, thrombocytopenia, pneumonia, and anemia.

***Discontinuation and dose reduction due to ARs***
Of the 250 patients treated with IMBRUVICA for MCL, seven (3%) discontinued treatment due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation included hemorrhage, pneumonia, and thrombocytopenia. Adverse reactions leading to dose reduction occurred in 6% of patients.

Adverse reactions from Study 1104 are described below in Table 1 to reflect exposure to IMBRUVICA in patients with MCL who received at least one prior therapy with a median treatment duration of 8.3 months.

**Table 1: Treatment-emergent adverse reactions reported in ≥ 10% of patients with MCL treated with 560 mg IMBRUVICA – Study 1104 (N = 111)**

| | | Frequency | |
|---|---|---|---|
| **System Organ Class** | **Adverse Reaction** | **All Grades (%)** | **Grades 3-4 (%)** |
| Infections and infestations | Pneumonia | 12 | 5 |
| | Urinary tract infection | 14 | 3 |
| | Sinusitis | 14 | 1 |
| | Upper respiratory tract infection | 26 | 0 |
| Blood and lymphatic system disorders | Neutropenia | 19 | 17 |
| | Thrombocytopenia | 21 | 12 |
| | Anemia | 15 | 10 |
| Metabolism and nutrition disorders | Dehydration | 14 | 4 |
| | Hyperuricemia | 17 | 5 |
| | Decreased appetite | 23 | 2 |
| Nervous system disorders | Dizziness | 14 | 0 |
| | Headache | 12 | 0 |
| Respiratory, thoracic and mediastinal disorders | Dyspnea | 28 | 4 |
| | Epistaxis | 11 | 0 |
| | Cough | 18 | 0 |
| Gastrointestinal disorders | Diarrhea | 53 | 5 |
| | Abdominal pain | 18 | 5 |
| | Vomiting | 23 | 0 |
| | Stomatitis | 13 | 1 |
| | Constipation | 28 | 0 |
| | Nausea | 32 | 1 |
| | Dyspepsia | 11 | 0 |
| Skin and subcutaneous tissue disorders | Rash | 16 | 2 |
| Musculoskeletal and connective tissue disorders | Muscle spasms | 14 | 0 |
| | Myalgia | 14 | 0 |
| | Arthralgia | 14 | 0 |
| | Back pain | 14 | 1 |
| | Pain in extremity | 12 | 0 |
| General disorders and administration site conditions | Pyrexia | 19 | 1 |
| | Fatigue | 43 | 5 |
| | Asthenia | 12 | 3 |
| | Edema peripheral | 30 | 2 |
| Injury, poisoning and procedural complications | Contusion | 18 | 0 |

***Serious adverse reactions***
In the phase 2 study, serious adverse reactions were reported in 60% of patients (treatment-emergent frequencies). Serious adverse reactions that occurred in greater than 2% of patients were atrial fibrillation (6%), pneumonia (5%), urinary tract infection (4%), abdominal pain (3%), subdural hematoma (3%), febrile neutropenia (3%), acute renal failure (3%), peripheral edema (3%), and pyrexia (3%).

Adverse reactions from Study MCL3001 are described below in Table 2 reflecting exposure to IMBRUVICA in patients with MCL who received at least one prior therapy, treated with a median treatment duration of 14.4 months.

**Table 2: Adverse reactions reported in patients with MCL treated with 560 mg IMBRUVICA – Study MCL3001 (n=139)**

| | | IMBRUVICA (n=139) | | Temsirolimus (n=139) | |
|---|---|---|---|---|---|
| **System Organ Class** | **Adverse Reactions** | **All Grades (%)** | **Grade 3 or 4 (%)** | **All Grades (%)** | **Grade 3 or 4 (%)** |
| Infections and infestations | Upper respiratory tract infection | 19 | 2 | 12 | 1 |
| | Pneumonia* | 14 | 10 | 19 | 12 |
| Eye disorders | Conjunctivitis | 12 | 0 | 5 | 0 |
| Cardiac disorders | Atrial fibrillation | 4 | 4 | 2 | 1 |
| Gastrointestinal disorders | Abdominal pain | 8 | 4 | 8 | 1 |
| Musculoskeletal and connective tissue disorders | Muscle spasms | 19 | 0 | 3 | 0 |

* Includes multiple adverse reaction terms.

**Chronic lymphocytic leukemia**
The data described below reflect exposure to IMBRUVICA in a single arm, open-label clinical study (Study PCYC-1102-CA) that included 51 patients and a randomized clinical study (Study PCYC-1112-CA) and three randomized clinical studies (Study PCYC 1115 CA, Study PCYC 1112 CA, and Study CLL3001) in patients with CLL (n=668).

The most commonly occurring adverse reactions in studies PCYC-1102-CA, PCYC-1112-CA, PCYC 1115 CA and CLL3001 (≥ 20%) were diarrhea, neutropenia, rash, musculoskeletal pain, hemorrhage (e.g., bruising), nausea, thrombocytopenia, and pyrexia.

The most common Grade 3/4 adverse reactions (≥ 5%) were: neutropenia, pneumonia, thrombocytopenia and febrile neutropenia.

***Discontinuation and dose reduction due to AEs***
Six percent of patients receiving IMBRUVICA in studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA and CLL3001 discontinued treatment due to adverse events. The most frequent adverse reactions leading to treatment discontinuation included pneumonia, atrial fibrillation, rash and hemorrhage. Adverse events leading to dose reduction occurred in approximately 6% of patients.

***Patients with previously untreated CLL***
***Single agent***
Adverse reactions described below in Table 3 reflect exposure to IMBRUVICA with a median duration of 17.4 months, which is approximately 2.5 times the median exposure to chlorambucil of 7.1 months in Study PCYC-1115-CA.

**Table 3: Adverse reactions reported in previously untreated patients with CLL treated with 420 mg IMBRUVICA - Study PCYC-1115-CA[a]**

| | IMBRUVICA (N=135) | | Chlorambucil (N=132) | |
|---|---|---|---|---|
| **System Organ Class**<br>**Adverse Reaction** | **All Grades (%)** | **Grade 3 or 4 (%)** | **All Grades (%)** | **Grade 3 or 4 (%)** |
| **Infections and infestations** | | | | |
| Skin infection* | 15 | 2 | 3 | 1 |
| Pneumonia* | 14 | 8 | 7 | 4 |

| | | | | |
|---|---|---|---|---|
| **Neoplasms benign, malignant, and unspecified (including cysts and polyps)** | | | | |
| Basal cell carcinoma | 9 | 1 | 2 | 0 |
| **Metabolism and nutrition disorders** | | | | |
| Hyponatremia | 7 | 3 | 1 | 0 |
| **Eye disorders** | | | | |
| Dry eye | 17 | 0 | 5 | 0 |
| Lacrimation increased | 13 | 0 | 6 | 0 |
| Vision blurred | 13 | 0 | 8 | 0 |
| Visual acuity reduced | 11 | 0 | 2 | 0 |
| **Cardiac disorders** | | | | |
| Atrial fibrillation | 6 | 1 | 1 | 0 |
| **Vascular disorders** | | | | |
| Hypertension* | 14 | 4 | 1 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 22 | 0 | 15 | 0 |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 42 | 4 | 17 | 0 |
| Stomatitis* | 14 | 1 | 4 | 1 |
| Dyspepsia | 11 | 0 | 2 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash* | 21 | 4 | 12 | 2 |
| Bruising* | 19 | 0 | 7 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal pain* | 36 | 4 | 20 | 0 |
| Arthralgia | 16 | 1 | 7 | 1 |
| Muscle spasms | 11 | 0 | 5 | 0 |
| **General disorders and administrative site conditions** | | | | |
| Peripheral edema | 19 | 1 | 9 | 0 |

[a] Subjects with multiple events for a given adverse reaction term are counted once only for each adverse reaction term.
* Includes multiple adverse reaction terms

***Patients with CLL who received at least one prior therapy***
***Single agent***
Adverse reactions described in Table 4 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.

**Table 4: Adverse reactions reported in patients with CLL treated with IMBRUVICA as single agent in Study PCYC-1112-CA[a]**

| | **IMBRUVICA (N=195)** | | **Ofatumumab (N=191)** | |
|---|---|---|---|---|
| **System Organ Class Adverse Reaction** | **All Grades (%)** | **Grade 3 or 4 (%)** | **All Grades (%)** | **Grade 3 or 4 (%)** |
| **Infections and infestations** | | | | |
| Upper respiratory tract infection | 16 | 1 | 10 | 2 |
| Pneumonia* | 15 | 10 | 13 | 9 |
| Sinusitis* | 11 | 1 | 6 | 0 |
| Urinary tract infection | 10 | 4 | 5 | 1 |
| Skin infection* | 7 | 2 | 3 | 1 |
| Sepsis* | 4 | 2 | 4 | 3 |
| **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 |

| | | | | |
|---|---|---|---|---|
| **Nervous system disorders** | | | | |
| Headache | 14 | 1 | 6 | 0 |
| Dizziness | 11 | 0 | 5 | 0 |
| **Eye disorders** | | | | |
| Vision blurred | 10 | 0 | 3 | 0 |
| **Cardiac disorders** | | | | |
| Atrial fibrillation | 5 | 3 | 1 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Epistaxis | 9 | 0 | 3 | 1 |
| **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 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash* | 24 | 3 | 13 | 0 |
| Bruising* | 21 | 0 | 4 | 0 |
| Petechiae | 14 | 0 | 1 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Musculoskeletal pain* | 28 | 2 | 18 | 1 |
| Arthralgia | 17 | 1 | 7 | 0 |
| **General disorders and administration site conditions** | | | | |
| Pyrexia | 24 | 2 | 15 | 1 |
| **Injury, poisoning and procedural complications** | | | | |
| Subdural hematoma | 1 | 0 | 0 | 0 |

[a] 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.

* 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.

**Long-term safety**

The long-term safety data over 5 years from 1178 patients (treatment-naïve CLL n=162, relapsed/refractory CLL n=646, and relapsed/refractory MCL n=370) treated with IMBRUVICA were analyzed. The median duration of treatment for CLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of patients receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of patients receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

**Postmarketing data**

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 6). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

| | |
|---|---|
| Very common | ≥ 1/10 (≥ 10%) |
| Common | ≥ 1/100 and < 1/10 (≥ 1% and < 10%) |
| Uncommon | ≥ 1/1000 and < 1/100 (≥ 0.1% and < 1%) |
| Rare | ≥ 1/10000 and < 1/1000 (≥ 0.01% and < 0.1%) |
| Very rare | < 1/10000, including isolated reports (< 0.01%) |
| Not known | Cannot be estimated from the available data. |

In Table 5, adverse reactions are presented by frequency category based on spontaneous reporting rates and by frequency category based on incidence in clinical trials or epidemiology studies, when known.

**Table 5: Adverse reactions identified during postmarketing experience with IMBRUVICA**

| System Organ Class<br>Adverse Reaction | Frequency Category Estimated from Spontaneous Reporting Rates | Frequency Category Estimated from Clinical Trials with IMBRUVICA |
|---|---|---|
| **Cardiac disorders** | | |
| Ventricular tachyarrhythmias*† | Rare | Common |
| Cardiac failure*† | Uncommon | Common |
| **Immune system disorders** | | |
| Interstitial lung disease*† | Uncommon | Common |
| **Metabolism and nutrition disorders** | | |
| Tumor lysis syndrome | Very rare | Common |
| **Hepatobiliary disorders** | | |
| Hepatic failure*† | Very rare | Not known |
| **Skin and subcutaneous tissue disorders** | | |
| Angioedema | Very rare | Uncommon |
| Erythema | Very rare | Common |
| Onychoclasis | Uncommon | Common |
| Panniculitis* | Rare | Uncommon |
| Stevens-Johnson syndrome | Rare | Not known |
| Urticaria | Very rare | Common |
| **Nervous system disorders** | | |
| Peripheral neuropathy* | Uncommon | Common |
| Cerebrovascular accident† | Uncommon | Uncommon |
| Transient ischemic attack | Rare | Uncommon |
| Ischemic stroke† | Rare | Rare |
| **Infections and Infestations** | | |
| Hepatitis B reactivation | Not known | Uncommon |

* Includes multiple adverse reaction terms.
† Includes events with fatal outcome.

**OVERDOSE**

***Symptoms and signs***

There are limited data on the effects of IMBRUVICA overdose. No Maximum Tolerated Dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, one healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic Properties**

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE27.

**Mechanism of action**

Ibrutinib is a potent, small-molecule 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 sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including MCL, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and B-cell CLL. BTK's pivotal role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

***Lymphocytosis***

Upon initiation of single agent 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 (66%) with CLL. This effect has also been observed in some patients (35%) with MCL treated with IMBRUVICA. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few

month of IMBRUVICA therapy and typically resolves within a median of 8.0 weeks in patients with MCL and 14 weeks in patients with CLL (range 0.1 to 104 weeks).

When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was infrequent

***In vitro platelet aggregation***
In an in vitro study, ibrutinib demonstrated inhibition of collagen induced platelet aggregation in samples from the cohorts of subjects with either renal dysfunction, those on warfarin, or healthy subjects. The magnitude of inhibition of collagen-induced platelet aggregation in the cohort of subjects on aspirin was less pronounced since collagen-induced platelet aggregation was already reduced without ibrutinib. Ibrutinib did not show meaningful inhibition of platelet aggregation for the 4 agonists adenosine diphosphate (ADP), arachidonic acid, ristocetin, and thrombin receptor-activating peptide 6 (TRAP 6) across any of these cohorts of subjects or healthy subjects.

**Effect on QT/QTc interval and cardiac electrophysiology**
The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomized, double blind thorough QT study with placebo and positive controls. At a supratherapeutic dose of 1680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same study, a concentration dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a $C_{max}$ of 719 ng/mL following the supratherapeutic dose of 1680 mg) that was considered not clinically relevant.

**Clinical studies**
***Mantle cell lymphoma***
The safety and efficacy of IMBRUVICA in MCL patients who received at least one prior therapy were evaluated in a single open-label, multi-center Phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range, 40 to 84 years), 77% were male and 92% were Caucasian. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater were excluded from the study. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior stem cell transplant. At baseline, 39% of patients had bulky disease (≥ 5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.
IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. The primary endpoint in this study was investigator-assessed overall response rate (ORR). Responses to IMBRUVICA are shown in Table 6.

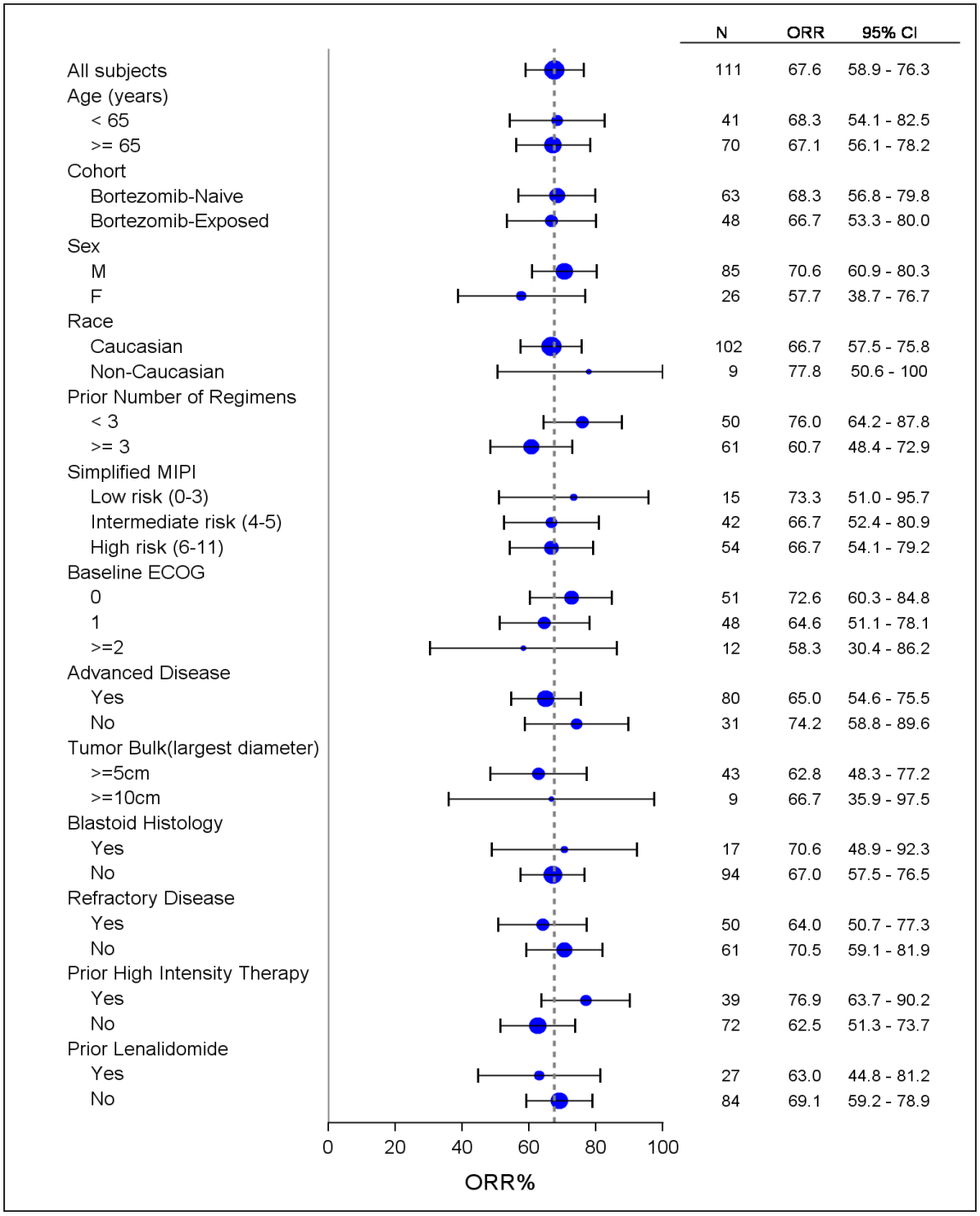
**Table 6: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with mantle cell lymphoma**

| | **Total N = 111** |
|---|---|
| ORR (%) | 67.6 |
| 95% CI (%) | (58.0, 76.1) |
| CR (%) | 20.7 |
| PR (%) | 46.8 |
| Median DOR (CR+PR) (months) | 17.5 (15.8, NR) |
| Median Time to Initial Response, months (range) | 1.9 (1.4-13.7) |
| Median Time to CR, months (range) | 5.5 (1.7, 11.5) |

CI = confidence interval; CR = complete response; PR = partial response; NR = not reached

The efficacy data was further evaluated by an Independent Review Committee (IRC) demonstrating an ORR of 69%, with a 21% CR rate and a 48% PR rate. The IRC estimated median DOR was 19.6 months.
The overall response to IMBRUVICA was independent of prior treatment including bortezomib and lenalidomide or underlying risk/prognosis, bulky disease, gender or age (Figure 1).

**Figure 1: Subgroup analysis of overall response rate by investigator assessment (Study PCYC-1104-CA; 560 mg)**




The safety and efficacy of IMBRUVICA were demonstrated in a randomized phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomized 1:1 to receive either IMBRUVICA orally at 560 mg once daily on a 21-day cycle or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34 to 88 years), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥ 5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progression-free survival (PFS) as assessed by IRC according to the revised IWG for non-Hodgkin's lymphoma (NHL) criteria showed a 57% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Efficacy results for Study MCL3001 are shown in Table 7 and the Kaplan-Meier curve for PFS in Figure 2.

**Table 7: Efficacy results in Study MCL3001**

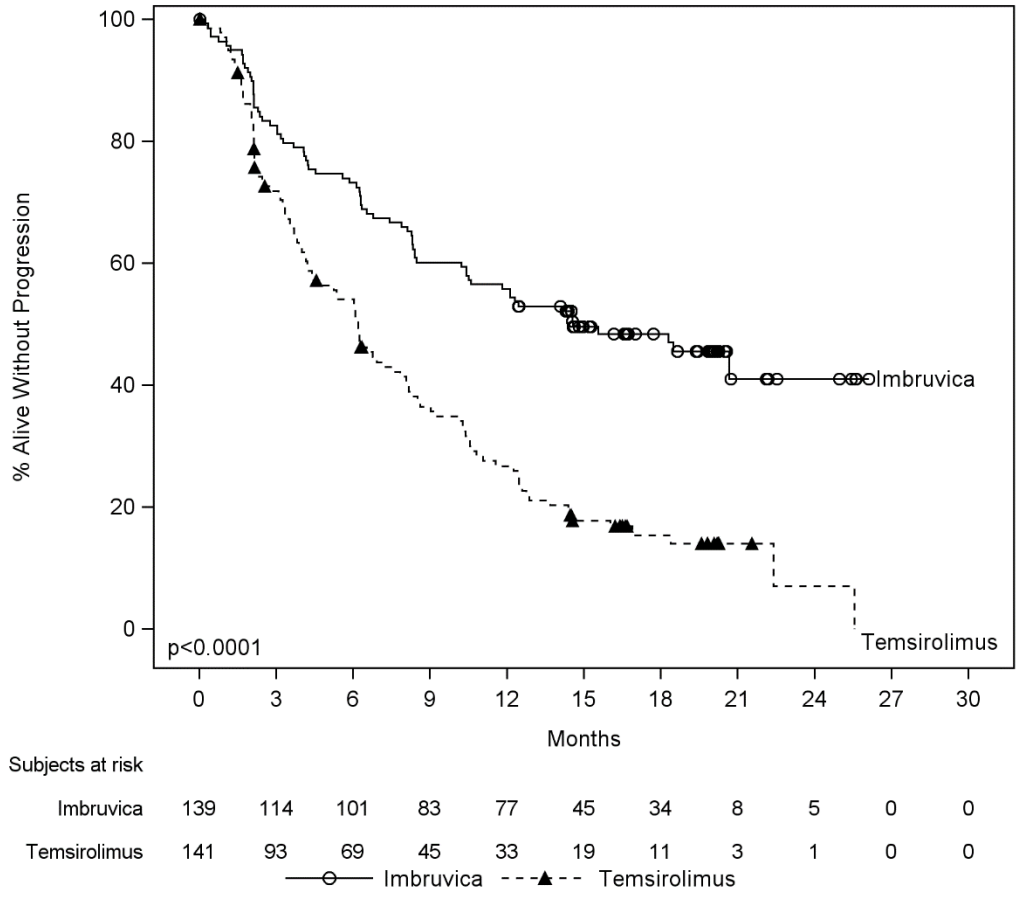
| Endpoint | IMBRUVICA N=139 | Temsirolimus N=141 |
|---|---|---|
| **Progression-Free Survival**[a] | | |
| Number of events (%) | 73 (52.5) | 111 (78.7) |
| Median Progression-Free Survival (95% CI), months | 14.6 (10.4, NE) | 6.2 (4.2, 7.9) |
| HR (95% CI) | 0.43 (0.32, 0.58) | |
| **Overall Response Rate (CR+PR)** | 71.9% | 40.4% |
| p-value | p<0.0001 | |

NE = not estimable; HR = hazard ratio; CI = confidence interval; CR = complete response; PR = partial response

[a] IRC evaluated.

A smaller proportion of patients treated with IMBRUVICA experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with IMBRUVICA versus temsirolimus (HR 0.27, p<0.0001).

**Figure 2: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study MCL3001**




***Chronic lymphocytic leukemia***

The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and two randomized, controlled studies.

**Patients with treatment-naïve CLL**

***Single agent***

***Study PCYC-1115-CA***

A randomized, multicenter, open-label phase 3 study of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients (n=269) were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety-one percent of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor ≥ 5 cm, 39% with baseline anemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin > 3500 mcg/L, 47% had a CrCL < 60 mL/min, 20% of patients presented with del 11q, 6% of patients presented with del 17p/tumor protein 53 (TP53) mutation, and 44% of patients presented with unmutated immunoglobulin heavy chain variable region (IGHV).

Progression-free survival (PFS) as assessed by IRC according to IWCLL criteria indicated an 84% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm. With a median follow-up of 18 months, the median PFS was not reached in the ibrutinib arm and was 19 months in the chlorambucil arm. Significant improvement in ORR was observed in the ibrutinib arm (82%) versus the chlorambucil arm (35%). The results from investigator and IRC assessments for PFS and ORR were consistent. Analysis of overall survival (OS) also demonstrated an 84% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 8 and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

There was a statistically significant sustained platelet or hemoglobin improvement in the ITT population in favor of ibrutinib vs. chlorambucil. In patients with baseline cytopenias, sustained hematologic improvement was: platelets 77% versus 43%; hemoglobin 84% versus 45% for ibrutinib and chlorambucil respectively.

**Table 8: Efficacy results in Study PCYC-1115-CA**

| Endpoint | IMBRUVICA N=136 | Chlorambucil N=133 |
|---|---|---|
| **Progression-Free Survival[a]** | | |
| Number of events (%) | 15 (11.0) | 64 (48.1) |
| Median (95% CI), months | Not reached | 18.9 (14.1, 22.0) |
| HR (95% CI) | 0.161 (0.091, 0.283) | |
| **Overall Response Rate[a] (CR+PR)** | 82.4% | 35.3% |
| p-value | <0.0001 | |
| **Overall Survival[b]** | | |
| Number of deaths (%) | 3(2.2) | 17 (12.8) |
| HR (95% CI) | 0.163 (0.048, 0.558) | |

CI = confidence interval; HR = hazard ratio; CR = complete response; PR = partial response

[a] IRC evaluated.

[b] Median OS not reached for both arms.

p < 0.005 for OS.

**Figure 3: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1115-CA**

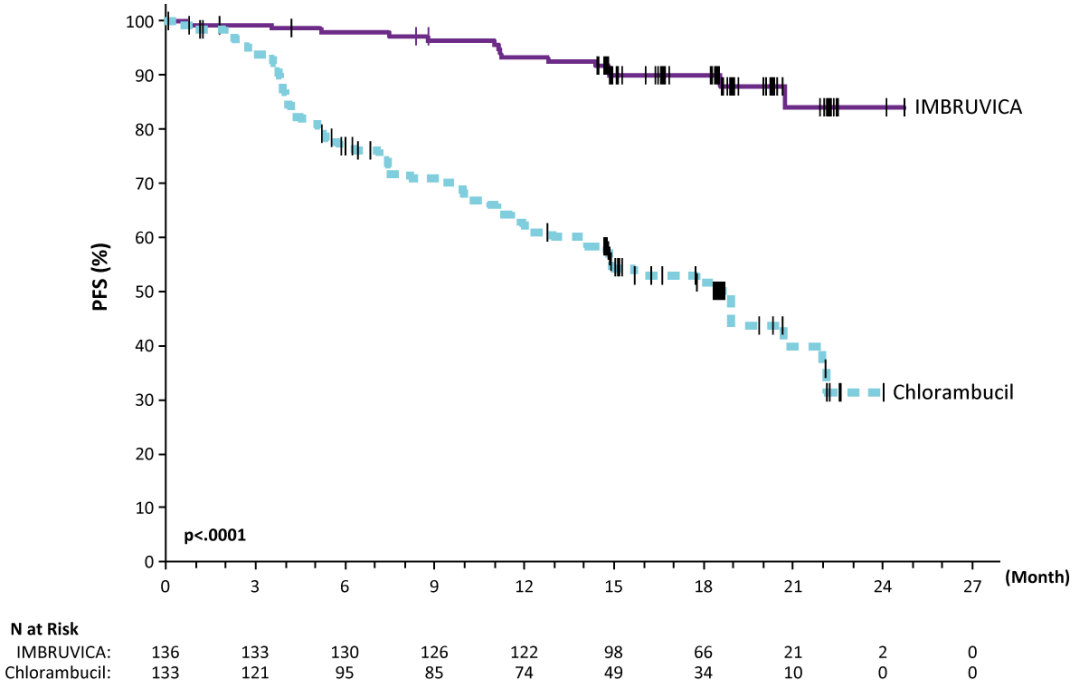
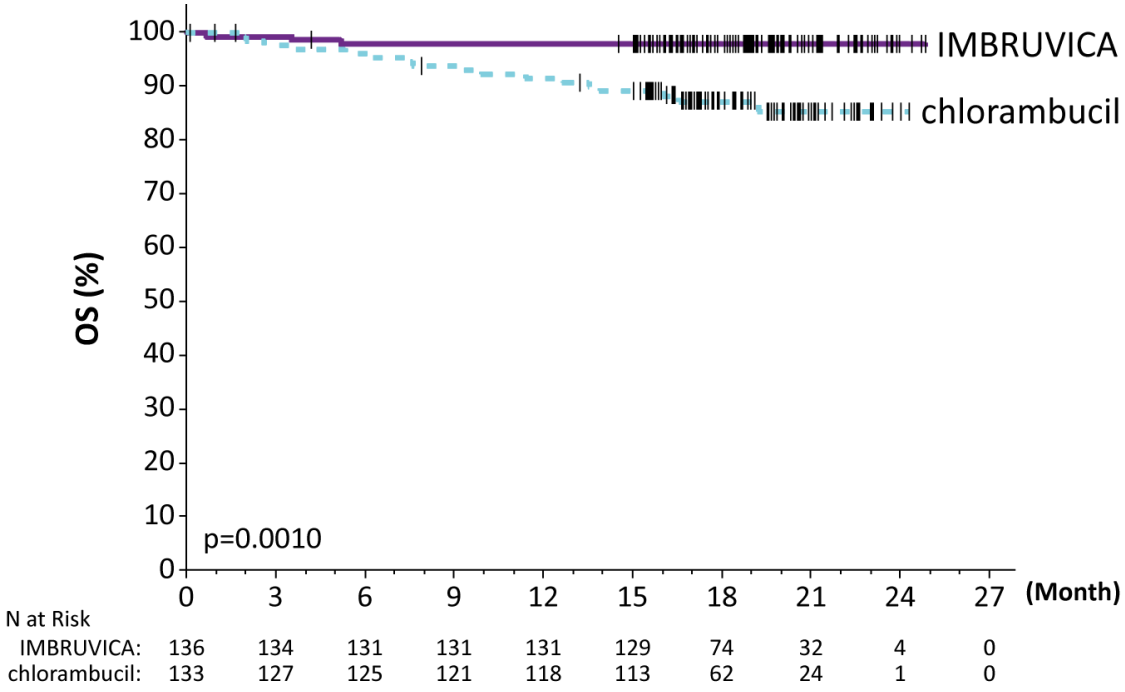



**Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA**



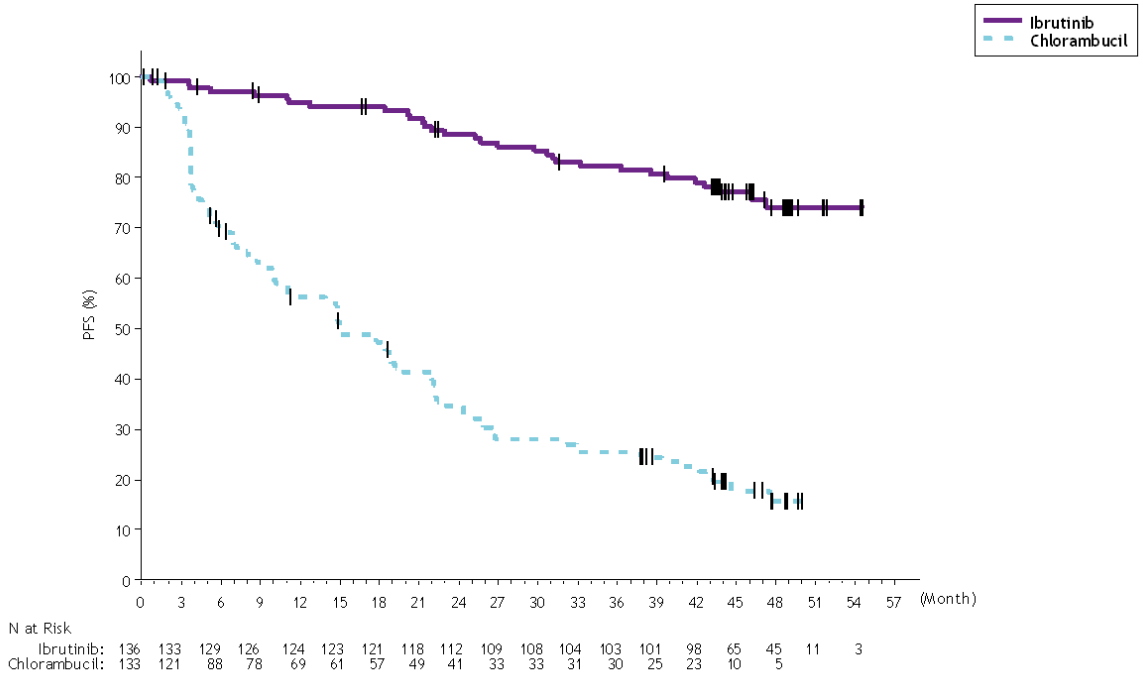

***Overall follow-up of 55 months (median of 48 months)***

With an overall follow-up of 55 months (median of 48 months) in Study PCYC-1115-CA and its extension study, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS was not reached in the IMBRUVICA arm and was 15 months [95% CI (10.22, 19.35)] in the chlorambucil arm; (HR = 0.14 [95% CI (0.09, 0.21)]). The 4-year PFS estimate was 73.9% in the IMBRUVICA arm and 15.5% in the chlorambucil arm, respectively. The updated Kaplan-Meier curve for PFS is shown in Figure 5. The investigator-assessed ORR was 91.2% in the IMBRUVICA arm versus 36.8% in the chlorambucil arm. The CR rate according

to IWCLL criteria was 16.2% in the IMBRUVICA arm versus 3.0% in the chlorambucil arm. At the time of long-term follow-up, a total of 73 subjects (54.9%) originally randomized to the chlorambucil arm subsequently received ibrutinib as cross-over treatment. The Kaplan-Meier landmark estimate for OS at 48-months was 85.5% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1115-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

**Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1115-CA with 55 Months Follow-up**




**Patients with CLL who received at least one prior therapy**

***Single agent***

***PCYC-1102-CA***

An open-label, multi-center study was conducted in 51 patients with CLL who received 420 mg once daily. IMBRUVICA was administered 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), including 92% with a prior nucleoside analog, 98% with prior rituximab, 86% with a prior alkylator, 39% with prior bendamustine and 20% with prior ofatumumab. At baseline, 39% of patients had Rai Stage IV, 45% had bulky disease (≥ 5 cm), 35% had del 17p, 31% had del 11q.

ORR was investigator-assessed according to the 2008 International Workshop on CLL (IWCLL) criteria. At a median duration of follow up of 16 months, responses to IMBRUVICA for the 51 patients are shown in Table 9.

**Table 9: Overall response rate in patients with chronic lymphocytic leukemia treated with 420 mg IMBRUVICA - Study PCYC-1102-CA (N = 51)**

| | |
|---|---|
| ORR (CR+PR) (95% CI) (%) | 78.4 (64.7, 88.7) |
| CR (%) | 3.9 |
| PR (%) | 74.5 |
| ORR including Partial Response with Lymphocytosis (PRL) (%) | 92.2 |
| Median DOR (CR+PR) | NR[1] |
| Median Time to Initial Response, months (range) | 1.8 (1.4, 12.2) |

CI = confidence interval; CR = complete response; PR = partial response

[1] 92.5% of responders were censored (i.e., progression free and alive) with a median follow up of 16.4 months.
NR: not reached

The efficacy data were further evaluated using IWCLL criteria by an IRC, demonstrating an ORR of 65% (95% CI: 50%, 78%), all partial responses. The DOR ranged from 4 to 24+ months. The median DOR was not reached.

***PCYC-1112-CA***

A randomized, multi-center, open-label Phase 3 study of IMBRUVICA versus ofatumumab was conducted in patients with CLL. 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 tumor ≥ 5 cm. Thirty-two percent of patients had deletion 17p (with 50% of patients having deletion 17p/TP53 mutation), 24% had 11q deletion, and 47% of patients had unmutated IGHV.

Progression free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. The results from investigator and IRC assessments for PFS were consistent. Analysis of OS demonstrated a 57% statistically significant reduction in the risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1112-CA are shown in Table 10.

**Table 10: Efficacy results in patients with chronic lymphocytic leukemia (Study PCYC-1112-CA)**

| Endpoint | IMBRUVICA N=195 | Ofatumumab N=196 |
|---|---|---|
| **Progression-Free Survival** | | |
| Median Progression-Free Survival, months | Not reached | 8.1 |
| HR (95% CI) | 0.215 (0.146; 0.317) | |
| **Overall Survival**[a] | | |
| HR (95% CI) | 0.434 (0.238; 0.789)[b] | |
| HR (95% CI) | 0.387 (0.216; 0.695)[c] | |
| **Overall Response Rate**[d,e] **(%)** | 42.6 | 4.1 |
| **Overall Response Rate including Partial Response with Lymphocytosis (PRL)**[d] **(%)** | 62.6 | 4.1 |

HR = hazard ratio; CI = confidence interval; PR = partial response

[a] Median OS not reached for both arms.

[b] Patients randomized to ofatumumab who progressed were censored when starting ibrutinib if applicable.

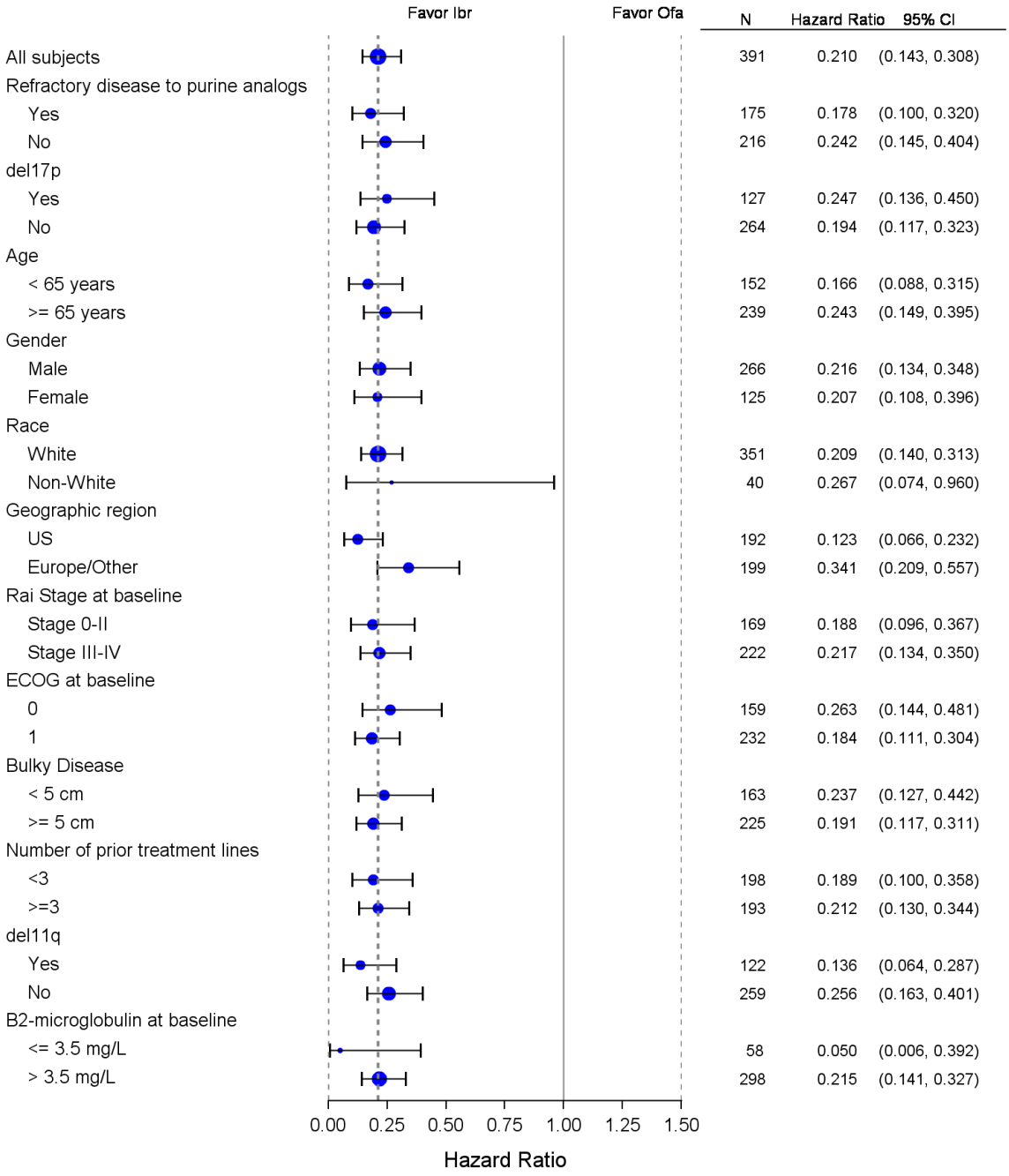
[c] Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of IMBRUVICA.

[d] Per IRC. Repeat CT scans required to confirm response.

[e] All PRs achieved. $p < 0.0001$ for ORR.

The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 6).

**Figure 6: Subgroup analysis of progression free survival by IRC (Study PCYC-1112; 420 mg)**




The Kaplan Meier curves for PFS and OS are shown in Figures 7 and 8, respectively.

**Figure 7: Kaplan Meier curve of progression free survival (ITT Population) in study PCYC 1112 CA**

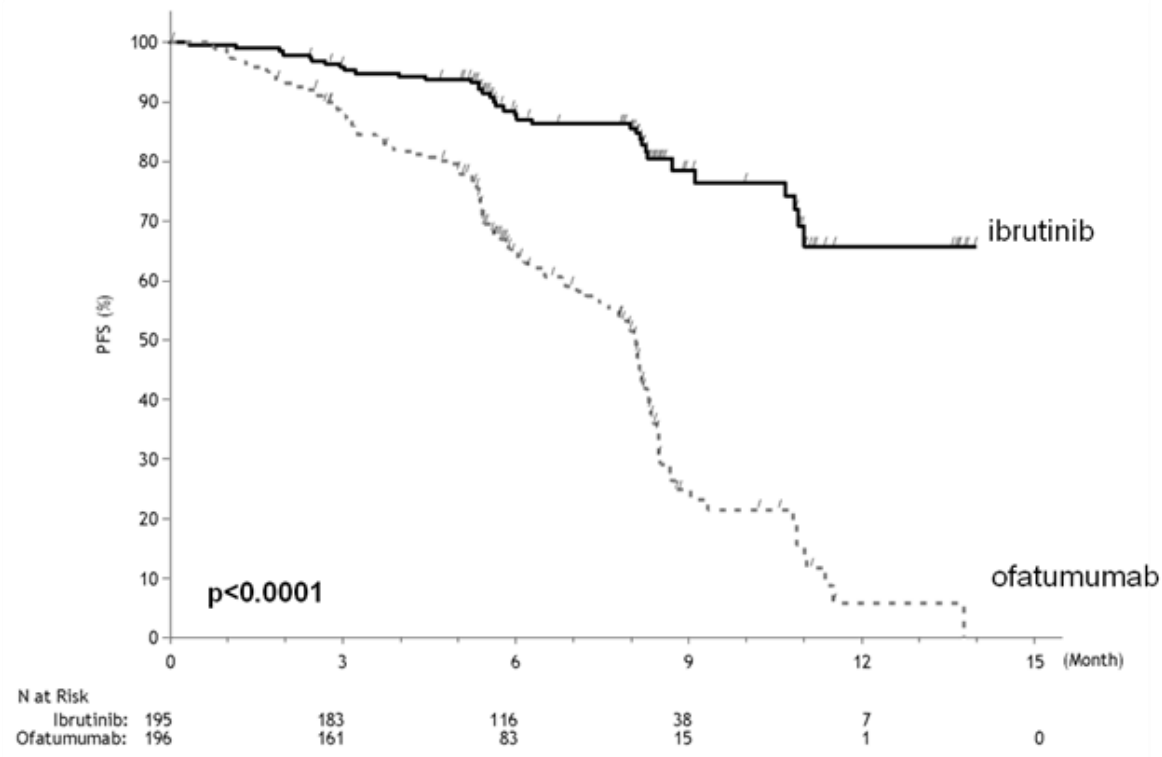
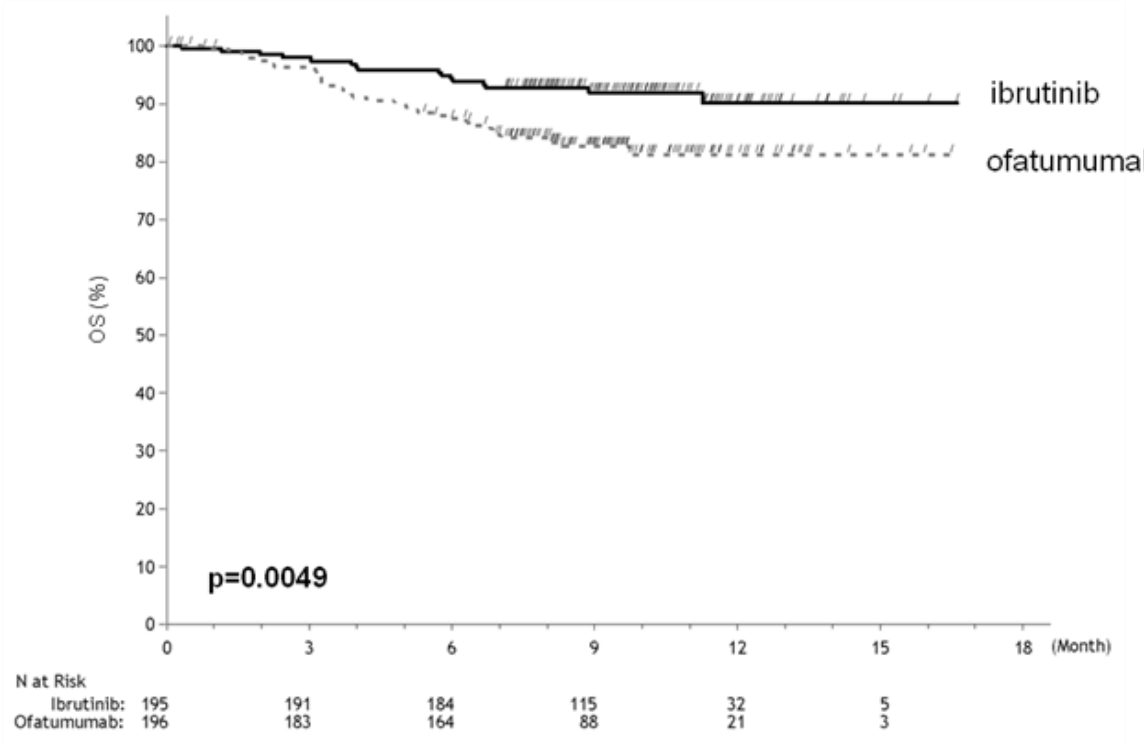



**Figure 8: Kaplan-Meier curve of overall survival (ITT Population) in study PCYC-1112-CA**



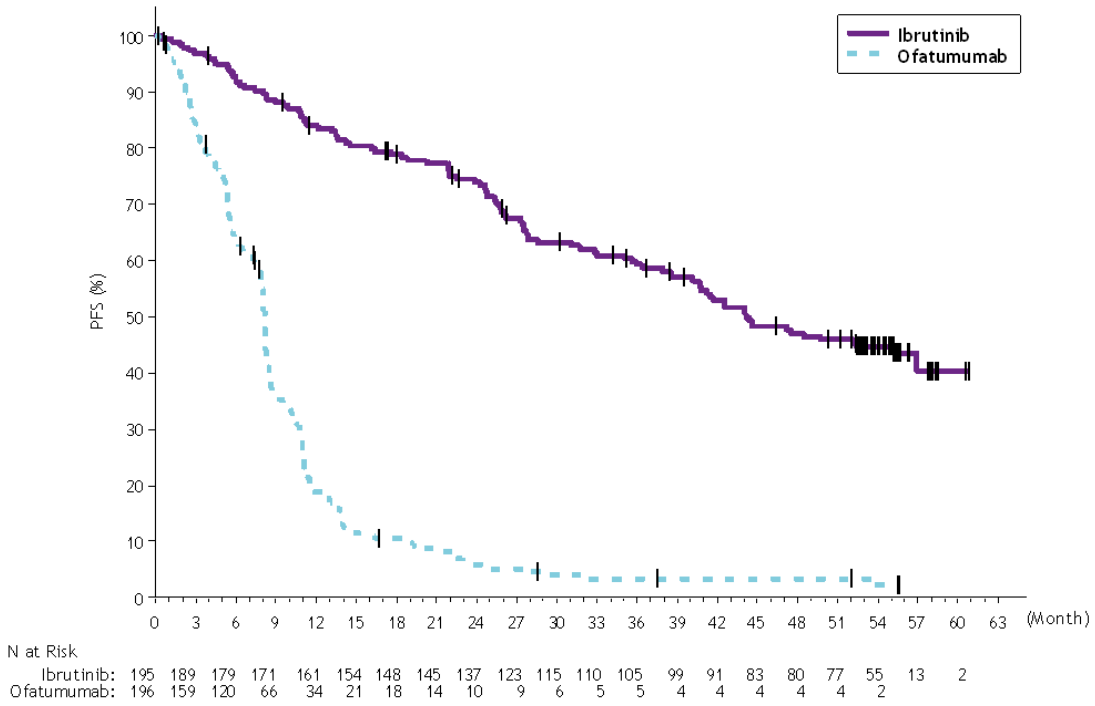

***Overall follow-up of 63 months (median of 56 months)***

With an overall follow-up of 63 months (median of 56 months) in Study PCYC-1112-CA, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.54, 56.87)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR = 0.14 [95% CI (0.11, 0.19)]. The updated Kaplan-Meier curve for PFS is shown in Figure 9. The investigator-assessed ORR in the IMBRUVICA arm was 87.2% versus 22.4%

in the ofatumumab arm. At the time of long-term follow-up, 133 (67.9%) of the 196 subjects originally randomized to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The Kaplan-Meier landmark estimate for OS at 60-months was 62.2% in the IMBRUVICA arm.

The treatment effect of ibrutinib in Study PCYC-1112-CA was consistent across high-risk patients with del 17p/TP53 mutation, del 11q, and/or unmutated IGHV.

**Figure 9: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) by Investigator in Study PCYC-1112-CA with 63 Months Follow-up**




***CLL with deletion 17p***

Study PCYC-1112-CA included 127 patients with CLL with deletion 17p. 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 deletion 17p are shown in Table 11.

**Table 11: Efficacy results in patients with CLL with deletion 17p**

| Endpoint | IMBRUVICA N=63 | Ofatumumab N=64 |
|---|---|---|
| **Progression-Free Survival** | | |
| Median Progression-Free Survival, months | Not reached | 5.8 |
| HR (95% CI) | 0.25 (0.14; 0.45) | |
| **Overall Response Rate**[a] | 47.6% | 4.7% |
| **Overall Response Rate including PRL** | 66.7% | 4.7% |

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

HR = hazard ratio; CI = confidence interval; PRL = partial response with lymphocytosis

***Overall follow-up of 63 months (median of 56 months)***

With an overall follow-up of 63 months (median of 56 months) in Study PCYC-1112-CA, the median investigator-assessed PFS in patients with del 17p according to IWCLL criteria was 40.6 months [95% CI (25.36, 44.55)] in the IMBRUVICA arm and 6.2 months [95% CI (4.63, 8.11)] in the ofatumumab arm, respectively; HR = 0.12, ([95% CI (0.07, 0.21)]. The investigator-assessed ORR in patients with del 17p in the IMBRUVICA arm was 88.9% versus 18.8% in the ofatumumab arm.

**Pharmacokinetic Properties**

**Absorption**

Ibrutinib is rapidly absorbed after oral administration with a median $T_{max}$ of 1 to 2 hours. Absolute bioavailability in fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng·h/mL and in patients at 420 mg with CLL is 732 ± 521 ng·h/mL (680 ± 517 ng·h/mL in subset of R/R patients). Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure ($AUC_{last}$) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

**Distribution**

Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The volume of distribution (Vd) was 683 L and the apparent volume of distribution at steady state ($V_{d,ss}$/F) is approximately 10000 L.

**Metabolism**

Ibrutinib is metabolized primarily by cytochrome P450, CYP3A4/5, 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 comparable to that of the parent drug.

*In vitro* studies indicated that CYP2D6 involvement in ibrutinib oxidative metabolism is < 2%. Moreover, as part of the human mass balance study, subjects genotyped as poor metabolizers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolizers. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

**Elimination**

Intravenous clearance was 62 and 76 L/h in fasted and fed condition, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2000 and 1000 L/h in fasted and fed condition, respectively. The half-life of ibrutinib is 4 to 6 hours.

After a single oral administration of radiolabeled [$^{14}$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.

**Special populations**

***Elderly (65 years of age and older)***

Population pharmacokinetics indicated that in older patients (67 to 81 years), a 14% higher ibrutinib exposure is predicted. Dose adjustment by age is not warranted.

***Pediatrics (18 years of age and younger)***

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

***Gender***

Population pharmacokinetics data indicated that gender does not significantly influence ibrutinib clearance from the circulation.

***Renal impairment***

Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific clinical studies have been conducted to date in subjects with impaired renal function. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis.

***Hepatic impairment***

Ibrutinib is metabolized in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of IMBRUVICA under fasting conditions. Ibrutinib $AUC_{last}$ increased 2.7-, 8.2- and 9.8-fold in subjects with mild (n=6; Child-Pugh class A), moderate (n = 10; Child-Pugh class B) and severe (n = 8; Child-Pugh class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound,last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

**NON-CLINICAL INFORMATION**
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. Effects on lymphoid tissue (lymphoid depletion) were also induced at HEDs ≥ 28 mg/kg/day in rats and ≥ 32 mg/kg/day in dogs. In rats, moderate pancreatic acinar cell atrophy was observed at HEDs ≥ 6 mg/kg/day. Mildly decreased trabecular and cortical bone was seen in rats administered HEDs ≥ 16 mg/kg/day for 13 weeks. All notable findings in rats and dogs fully or partially reversed following recovery periods of 6 to 13 weeks.

**Carcinogenicity and Mutagenicity**
Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2000 mg/kg/day resulting in exposures approximately 23 (males) to 37 (females) times higher than the exposure in humans at a dose of 560 mg daily.
Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice.

In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg. At a dose of ≥ 40 mg/kg/day, ibrutinib was associated with decreased foetal weights (AUC ratio of ≥ 5.6 as compared to daily dose of 560 mg in patients). Consequently, the foetal NOAEL was 10 mg/kg/day (approximately 1.3 times the AUC of ibrutinib at a dose of 560 mg daily).
In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day). Consequently, the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily).

**Fertility**
No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (HED 16 mg/kg/day).

**PHARMACEUTICAL INFORMATION**
**List of Excipients**
**Capsules**
IMBRUVICA capsules contain the following excipients:
croscarmellose sodium,
magnesium stearate,
microcrystalline cellulose,
sodium lauryl sulfate.
The capsule shell contains gelatin and titanium dioxide (E171).

Black Printing Ink:
iron oxide black (E172)
propylene glycol
shellac glaze

**Incompatibilities**
Not applicable

**Shelf Life**
Shelf-life before opening: 24 months.
Shelf-life after opening: 45 days

**Storage Conditions**
Keep out of the sight and reach of children.
Store below 30°C.

**Nature and Contents of Container**
**Capsules**
IMBRUVICA capsules are supplied in a white high-density polyethylene (HDPE) bottle with a child-resistant closure.
Each HDPE bottle with a polypropylene closure contains 90 hard capsules.
Not all pack sizes may be marketed.

**Instructions for Disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

**HOW SUPPLIED**
Imbruvica capsule 140 mg
Box, 1 bottle @ 90 capsules
Reg. No.: DKI1951100101A1

**HARUS DENGAN RESEP DOKTER**

Manufactured by Catalent CTS, LLC 10245 Hickman Mills Drive, Kansas City, MO, 64137, USA
Primary and secondary Packaged by AndersonBrecon Inc 4545 Assembly Drive, Rockford, IL 61109 USA
Finish batch released by Janssen Supply Group, LLC, 200 Tournament Drive Horsham, PA 19044 USA
Imported and distributed by PT Soho Industri Pharmasi
Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920 – Indonesia - (021) 460-5550
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935-3935

Based on CCDS CCDS v.29 21Aug20

**Informasi Produk untuk Pasien**
**IMBRUVICA® (Ibrutinib)**
**140 mg Kapsul**

**Baca informasi ini secara lengkap dan seksama sebelum Anda mulai menggunakan obat ini.**
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau tenaga medis professional Anda.
- Obat ini telah diresepkan untuk Anda saja. Jangan berikan kepada orang lain. Hal tersebut dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka sama seperti Anda.
- Jika Anda menemukan efek samping serius atau jika Anda menemukan efek samping yang tidak tercantum dalam informasi produk ini, laporkan kepada dokter, perawat atau apoketer Anda.

**Apa yang ada dalam informasi produk ini**


## 1. Apakah Imbruvica itu dan digunakan untuk apa

Imbruvica adalah obat anti kanker yang mengandung zat aktif ibrutinib. Imbruvica digunakan untuk pengobatan kanker darah berikut pada orang dewasa:
- *Mantle Cell Lymphoma* (MCL), yaitu jenis kanker yang mempengaruhi kelenjar getah bening;
- *Chronic Lymphocytic Leukemia* (CLL), yaitu jenis kanker yang mempengaruhi sel darah putih yaitu limfosit yang juga mempengaruhi kelenjar getah bening. IMBRUVICA digunakan pada pasien yang sebelumnya belum pernah mendapatkan perawatan untuk CLL atau ketika penyakit tersebut kembali atau belum ada respon terhadap pengobatan.
- *Chronic Lymphocytic Leukemia* dengan penghapusan 17p, yaitu jenis CLL di mana sel-sel kanker memiliki perubahan DNA tertentu.

IMBRUVICA bekerja dengan menghambat protein didalam tubuh yang membantu kehidupan dan pertumbuhan sel kanker. Protein ini disebut *Bruton's tyrosine kinase*. Dengan menghambat protein ini, IMBRUVICA dapat membunuh dan mengurangi jumlah sel kanker dan juga dapat memperlambat penyebaran kanker.

## 2. Apa saja yang harus Anda ketahui sebelum menggunakan Imbruvica

**Jangan gunakan IMBRUVICA**
- Jika Anda alergi terhadap ibrutinib atau salah satu bahan lain dari obat ini (lihat bagian **apa isi IMBRUVICA**).
- Jika Anda menggunakan obat-obatan herbal yang bernama St. John's Wort, yang digunakan untuk depresi.

Jika Anda tidak yakin, tanyakan kepada dokter Anda sebelum menggunakan IMBRUVICA. Jika Anda memiliki salah satu dari tanda-tanda reaksi alergi (gatal-gatal, kesulitan bernapas, atau pembengkakan pada wajah, bibir, lidah, atau tenggorokan Anda) ketika menggunakan IMBRUVICA, segera dapatkan bantuan medis.

**Peringatan dan Perhatian**
Bicaralah dengan dokter atau tenaga medis profesional Anda sebelum menggunakan Imbruvica:
- jika Anda pernah memiliki memar yang tidak biasa atau perdarahan atau pada setiap obat atau suplemen yang meningkatkan risiko perdarahan (lihat **Obat-obat lain dan IMBRUVICA**)

- jika Anda pernah mengalami masalah dengan irama jantung atau gagal jantung berat, atau jika Anda merasakan hal-hal berikut: denyut jantung Anda cepat dan tidak teratur, pening, pusing, sesak napas, ketidaknyamanan di dada, atau Anda pingsan
- jika Anda memiliki masalah pada hati atau ginjal
- jika Anda memiliki tekanan darah tinggi
- jika Anda baru saja menjalani operasi apapun, terutama jika hal ini dapat mempengaruhi bagaimana Anda menyerap makanan atau obat-obatan melalui perut atau usus
- jika Anda berencana untuk menjalani operasi apapun - dokter Anda akan meminta Anda untuk berhenti menggunakan IMBRUVICA untuk waktu yang singkat.

Jika salah satu di atas terjadi pada Anda atau Anda tidak yakin, tanyakan kepada dokter atau tenaga medis profesional Anda sebelum menggunakan IMBRUVICA.

Saat menggunakan IMBRUVICA, beritahu dokter Anda secepatnya jika Anda atau orang lain menyadari Anda mengalami kehilangan ingatan, sulit berpikir, kesulitan berjalan atau kehilangan penglihatan, keadaan-keadaan ini mungkin tapi sangat jarang terjadi yang disebabkan oleh infeksi otak serius yang dapat berakibat fatal (*Progressive Multifocal Leukoencephalopathy* atau PML).

**Tes dan pemeriksaan sebelum dan selama pengobatan**
*Tumour lysis syndrome* (TLS): konsentrasi bahan kimia pada darah yang tidak lazim yang disebabkan oleh kerusakan sel kanker secara cepat yang terjadi selama pengobatan kanker dan bahkan kadang tanpa pengobatan. Hal ini mungkin menyebabkan perubahan pada fungsi ginjal, detak jantung yang tidak normal atau kejang. Dokter Anda atau ahli kesehatan lain akan melakukan tes darah untuk menguji TLS.
Tes laboratorium menunjukkan bahwa darah Anda mengandung lebih banyak sel darah putih (disebut "*lymphocytes*"), dalam beberapa minggu pertama pengobatan. Hal ini sangat diharapkan dan dapat berlangsung selama beberapa bulan. Ini tidak berarti bahwa kanker darah Anda semakin parah. Dokter Anda akan memeriksa jumlah darah Anda sebelum atau selama pengobatan dan dalam kasus yang jarang mereka harus memberikan obat lain. Bicarakan dengan dokter Anda mengenai hasil tes Anda.

**Anak-anak dan remaja**
IMBRUVICA tidak digunakan untuk siapapun dengan usia kurang dari 18 tahun karena belum ada penelitian pada usia tersebut.

**Obat-obat lain dan IMBRUVICA**
Beritahu dokter, atau tenaga medis profesional Anda jika Anda sedang atau baru saja menggunakan obat lain. Termasuk obat yang diperoleh tanpa resep dokter dan obat-obat herbal dan supplemen. Karena IMBRUVICA dapat mempengaruhi cara kerja obat lain. Atau, obat-obat lain dapat mempengaruhi cara kerja IMBRUVICA.

**IMBRUVICA membuat Anda mudah mengalami pendarahan.** Beritahu dokter atau tenaga medis profesional Anda jika Anda sedang atau baru saja menggunakan obat lain yang dapat meningkatkan risiko perdarahan, termasuk menggunakan:
- aspirin dan non-steroidal anti-inflammatori (NSAIDS) seperti ibuprofen atau naproxen
- pengencer darah seperti warfarin, heparin atau obat lain untuk pembekuan darah
- supplement yang dapat meningkatkan risiko perdarahan seperti minyak ikan dan vitamin E.

Efek dari IMBRUVICA atau obat-obatan lain dapat terpengaruh jika Anda menggunakan IMBRUVICA bersama dengan salah satu obat-obatan berikut. **Beritahukan dokter anda jika anda sedang menggunakan**:
- antibiotik untuk pengobatan infeksi bakteri – clarithromisin, telithromisin, ciprofloksasin atau erythromisin dan rifampisin
- obat untuk infeksi jamur – ketokonazol, itrakonazole, fluconazole atau voriconazole
- obat untuk infeksi HIV – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir atau fosamprenavir
- obat untuk mencegah mual dan muntah yang berhubungan dengan kemoterapi – aprepitant
- obat untuk depresi – nefazodone
- obat-obat kinase inhibitor untuk pengobatan kanker lain – crizotinib, imatinib

- obat-obat calcium channel blockers untuk tekanan darah tinggi atau sesak dada – diltiazem, verapamil
- obat-obat statin untuk pengobatan kolesterol – rosuvastatin
- obat-obat jantung/anti-arrhythmia - amiodarone, dronedarone
- obat-obat untuk mencegah kejang atau pengobatan epilepsi atau obat-obat untuk mengobati kondisi yang menyakitkan pada wajah yang disebut *trigeminal neuralgia* – carbamazepine, phenytoin
- obat herbal, seperti untuk depresi - *St. John's Wort*.

Jika Anda sedang menggunakan digoxin, obat yang digunakan untuk penyakit jantung, atau metotreksat, obat yang digunakan untuk mengobati kanker lain dan untuk mengurangi aktivitas sistem kekebalan tubuh (misalnya, untuk rheumatoid arthritis atau psoriasis), harus diminum minimal 6 jam sebelum atau setelah menggunakan IMBRUVICA.

Tanyakan kepada dokter Anda jika Anda tidak yakin apakah obat Anda adalah salah satu yang tercantum di atas. Cari tahu obat yang Anda gunakan. Simpan daftar obat-obat Anda dan tunjukkan ke dokter atau tenaga medis profesional Anda ketika Anda mendapatkan obat baru.

**IMBRUVICA dengan makanan**
**Jangan menggunakan IMBRUVICA dengan jeruk bali atau jeruk Seville** - termasuk memakannya, meminum jusnya, atau menggunakan suplemen yang mungkin mengandung buah tersebut. Hal ini dapat meningkatkan jumlah IMBRUVICA dalam darah Anda.

**Kehamilan, menyusui dan kesuburan**
Jangan hamil saat Anda menggunakan IMBRUVICA.

Jika Anda sedang hamil, atau berpikir mungkin saya hamil atau berencana untuk hamil, tanyakan kepada dokter atau tenaga medis profesional Anda untuk sarannya sebelum menggunakan IMBRUVICA.

- Jangan menggunakan IMBRUVICA selama hamil.

Tidak ada informasi keamanan IMBRUVICA pada wanita hamil.

Wanita usia subur harus menggunakan metode yang efektif dalam pengendalian kehamilan selama dan sampai satu bulan setelah menerima IMBRUVICA untuk menghindari hamil saat pengobatan dengan IMBRUVICA. Jika menggunakan kontrasepsi hormonal seperti pil KB atau alat kontrasepsi, metode penghalang kontrasepsi (misalnya kondom) juga harus digunakan. Periode waktu setelah pengobatan dengan IMBRUVICA dimana apakah aman untuk kehamilan belum diketahui.

- Segera beritahu Dokter Anda jika Anda sedang hamil.
- Jangan menyusui jika Anda sedang menggunakan IMBRUVICA.

Jangan melakukan hubungan seksual atau menyumbangkan sperma selama menggunakan IMBRUVICA dan selama 3 bulan setelah pengobatan dihentikan. Gunakan kondom dan jangan menyumbangkan sperma selama pengobatan dan selama 3 bulan setelah pengobatan selesai. Jika Anda berencana untuk melakukan hubungan seksual, bicaralah dengan dokter atau tenaga medis profesional Anda sebelum menggunakan IMBRUVICA.

**Mengemudi dan menggunakan mesin**
Anda mungkin akan merasa letih atau lemah setelah menggunakan IMBRUVICA, yang dapat mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan peralatan atau mengoperasikan mesin.

## 3. Bagaimana cara menggunakan Imbruvica

- Gunakan IMBRUVICA seperti yang diresepkan oleh dokter atau tenaga medis professional Anda. Jangan merubah dosis atau berhenti menggunakan IMBRUVICA sampai dokter Anda memberitahukan kepada Anda.
- Telan kapsul IMBRUVICA dengan segelas air. Jangan membuka, mematahkan atau mengunyah kapsul. Jangan mematahkan kapsul.

- Gunakan IMBRUVICA pada waktu yang sama setiap hari**.**

Minum banyak cairan untuk menjaga Anda tetap terhidrasi saat menggunakan IMBRUVICA. Ini akan membantu ginjal Anda terus berfungsi dengan baik.

Jangan pernah memberikan IMBRUVICA kepada orang lain, bahkan jika mereka memiliki pengobatan yang sama dengan Anda

Berapa banyak digunakan

*Mantle Cell Lymphoma* (MCL)
Dosis yang dianjurkan dari IMBRUVICA adalah 560 mg sekali sehari.
*Chronic Lymphocytic Leukemia* (CLL)
Dosis yang dianjurkan dari IMBRUVICA 420 mg sekali sehari.

**Apa yang harus dilakukan jika Anda lupa menggunakan imbruvica**
Jika Anda lupa menggunakannya, anda dapat menggunakannya sesegera mungkin pada hari yang sama dengan kembali ke jadwal normal untuk hari berikutnya. Jangan menggunakan dosis ganda untuk menggantikan dosis yang terlewat. Hubungi dokter atau tenaga medis profesional Anda jika Anda tidak yakin apa yang harus dilakukan.

**Apa yang harus dilakukan jika Anda menggunakan lebih dari yang seharusnya**
Jika Anda menggunakan IMBRUVICA lebih dari yang seharusnya, hubungi dokter atau tenaga medis profesional Anda segera.

**Jika Anda berhenti menggunakan IMBRUVICA**
Jangan berhenti meminum Imbruvica kecuali dokter menyuruh Anda. Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan pada dokter, apoteker atau perawat Anda.

## 4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, Imbruvica dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.
Efek samping berikut dapat terjadi dengan obat ini: Hentikan menggunakan Imbruvica dan beritahukan dokter Anda segera jika Anda menyadari efek samping berikut terjadi:
Apabila terjadi gatal-gatal dan ruam, kesulitan bernafas, bengkak pada wajah, bibir, lidah atau tenggorokan – Anda mungkin mengalami reaksi alergi terhadap obat ini.
Beritahukan dokter Anda segera jika Anda menyadari efek samping berikut terjadi:

**Sangat sering terjadi** (terjadi pada lebih dari pada 1 dari 10 orang)
- Demam, panas dingin, sakit pada area badan, merasa kelelahan, gejala flu, napas pendek – gejala-gejala ini mungkin disebabkan oleh gejala infeksi (bakteri, virus atau fungi). Termasuk gejala infeksi di hidung, sinus atau tenggorokan (infeksi saluran pernapasan atas), atau paru-paru, atau kulit.
- Memar

**Sering terjadi** (terjadi pada 1 dari 10 orang)
- Infeksi parah di seluruh badan (sepsis)
- Infeksi saluran kemih
- Mimisan, bercak merah atau keunguan yang disebabkan pendarahan di bawah kulit, adanya darah pada feses atau urin, haid yang lebih banyak dari biasanya, pendarahan yang sulit berhenti – gejalan ini mungkin tanda-tanda serius adanya pendarahan internal dalam saluran cerna, usus atau otak.
- Denyut jantung yang cepat, denyut jantung yang terlewat, denyut yang lemah atau tidak stabil (gejala atrial fibrilasi)
- Peningkatan jumlah atau proporsi sel darah putih pada tes darah.
- Jumlah sel darah putih yang rendah disertai dengan demam (*febrile neutropenia*)

- Konsentrasi bahan kimia pada darah yang tidak lazim yang disebabkan oleh kerusakan sel kanker secara cepat yang terjadi selama pengobatan kanker dan bahkan kadang tanpa pengobatan (*tumour lysis syndrome*)
- Kenker kulit non-melanoma, paling sering adalah kanker sel squamos dan sel basal.
- Pusing
- Penglihatan kabur
- Tekanan darah tinggi
- Kulit kemerahan
- Konsentrasi "asam urat" yang tinggi pada darah, yang dapat menyebabkan rematik.
- Inflamasi pada paru yang dapat berakibat pada kerusakan permanen.
- Kerusakan pada kuku.
- gagal jantung, yang membuat Anda sesak napas dan dapat menyebabkan kaki menjadi bengkak

**Jarang terjadi** (terjadi pada 1 dari 100 orang)
- Peningkatan jumlah sel darah putih yang mengakibatkan sel saling bergumpal
- Reaksi alergi, kadang berat, termasuk pembengkakan pada wajah, bibir, mulut, lidah atau tenggorokan, sulit menelan atau bernapas, ruam gatal.
- Episode sementara dari gangguan fungsi neurologis yang disebabkan oleh hilangnya alirah darah, stroke.

**Efek samping yang sering terjadi lainnya**
- Sariawan
- Sakit kepala
- Konstipasi
- Mual atau muntah
- Diare
- Ruam kulit
- Nyeri pada lengan atau kaki
- Nyeri punggung atau nyeri sendi
- Kram otot, nyeri atau kejang pada kram otot, sakit atau kejang
- Jumlah sel yang membantu pembekuan darah yang rendah (trombosit), jumlah sel darah putih yang sangat rendah pada tes darah.
- Bengkak pada tangan, pergelangan kaki, atau telapak kaki.

**Belum diketahui frekuensi kejadiannya**
- Gagal hati, termasuk kejadian yang berakibat fatal
- Ruam terus menerus yang disertai dengan kulit melepuh dan mengelupas di sekitar mulut, hidung, mata dan alat kelamin (Steven-Johnson syndrome).

**Pelaporan efek samping**
Jika Anda mendapat efek samping termasuk efek samping yang tidak tercantum dalam leaflet ini, beritahukan dokter, apotkeker, atau perawat Anda. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut keamanan obat ini.

## 5. Bagaimana cara menyimpan Imbruvica

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan gunakan Imbruvica setelah tanggal kadaluarsa yang tertera pada karton dan label botol setelah kata EXP. Tanggal kadaluarsa mengacu pada hari terakhir dari bulan itu
- Jangan bekukan IMBRUVICA.
- Simpan pada suhu di bawah $30^0$C.
- Jangan membuang obat apapun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

## 6. Isi produk dan informasi lainnya

**Apa isi IMBRUVICA**
*Kapsul*
- Zat aktif adalah ibrutinib. Tiap kapsul mengandung 140 mg ibrutinib.

Bahan lain adalah croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, gelatin dan titanium dioxide (E171). Tinta cetak mengandung iron oxide black (E172), propylene glycol dan shellac glaze.

**Seperti apa IMBRUVICA dan isi kemasan**
*Kapsul*
Kapsul keras berwarna putih buram, dengan "ibr 140 mg" dicetak dengan tinta hitam.
IMBRUVICA tersedia dalam botol berisi 90 kapsul.

Reg. No.: DKI1951100101A1

**HARUS DENGAN RESEP DOKTER**

**Pemilik Izin Edar**
PT Soho Industri Pharmasi
Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920, Indonesia – phone (021) 460-5550
Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935

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