



# IMBRUVICA<sup>®</sup>

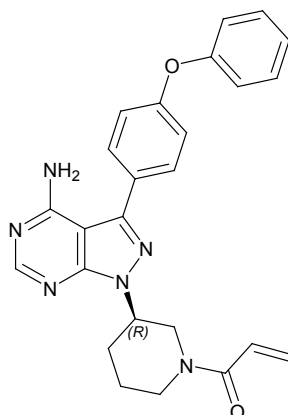
## ibrutinib

### PRODUCT INFORMATION

#### NAME OF THE MEDICINE

The chemical name of the ibrutinib is 1 [(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

Ibrutinib has the following chemical structure:



Molecular formula:  $C_{25}H_{24}N_6O_2$   
CAS Registry Number: 936563-96-1

Molecular weight: 440.50

#### DESCRIPTION

IMBRUVICA is supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque, size 0, hard gelatin capsule is marked with "ibr 140 mg" in black ink.

The characterization data demonstrate that ibrutinib at pH 1.2 is considered slightly soluble and at pH 3 to 8 ibrutinib is considered practically insoluble as defined by USP and European Pharmacopoeia nomenclature. Ibrutinib is non-hygroscopic and the melting onset temperature is 149-158 °C. The drug substance has one ionizable group, the protonated pyrimidine moiety, with a pKa of 3.74 in an aqueous solution with methanol as a co-solvent.

## PHARMACOLOGY

### Pharmacodynamics

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

#### Mechanism of action

Ibrutinib is a 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 signalling 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 CLL/SLL. BTK's pivotal role in signalling 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 B cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*.

#### Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e.,  $\geq 50\%$  increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (35%) with MCL treated with ibrutinib. 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 weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in patients with MCL and 18.7 weeks in patients with CLL/SLL.

A large increase in the number of circulating lymphocytes (e.g.,  $>400 \times 10^9/L$ ) has been observed in some patients.

### Pharmacokinetics

#### 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  $\pm$  standard deviation)  $953 \pm 705$  ng·h/mL. Administration with food increases ibrutinib exposure approximately 2 fold compared to administration after overnight fasting.

#### 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 apparent volume of distribution at steady state ( $V_{d,ss}/F$ ) is approximately 10000 L.

#### Metabolism

Ibrutinib is metabolised primarily by cytochrome P450, CYP3A4, 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, two subjects genotyped as poor metabolisers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolisers. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

## **Elimination**

Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. After a single oral administration of radiolabeled [<sup>14</sup>C] ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the faeces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine, with the remainder of the dose being metabolites.

## **Additional information on special populations**

### *Paediatrics (18 years of age and younger)*

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

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

Population pharmacokinetics indicated that age 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. In a dedicated hepatic impairment study in non-cancer patients administered a single dose of 140 mg of IMBRUVICA, preliminary data showed an approximate 4, 8, and 9 fold increase in ibrutinib exposure in subjects with mild (n=6), moderate (n=10) and severe (n=8) 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. An increase in unbound ibrutinib exposure is estimated to be 4, 9, and 13 fold in subjects with mild, moderate, and severe hepatic impairment, respectively.

### *Gender*

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

### *Race*

There are insufficient data to evaluate the potential effect of race on ibrutinib pharmacokinetics.

### *Body weight*

Population pharmacokinetics data indicated that body weight (range: 41-146 kg; mean [SD]: 83 (19) kg) had a negligible effect on ibrutinib clearance.

## CLINICAL TRIALS

### Mantle Cell Lymphoma

The safety and efficacy of ibrutinib in MCL patients who received at least one prior therapy were evaluated in a single open label, multi-centre 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. 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 ( $\geq 5$  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.

Ibrutinib was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumour 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 1.

**Table1: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma**

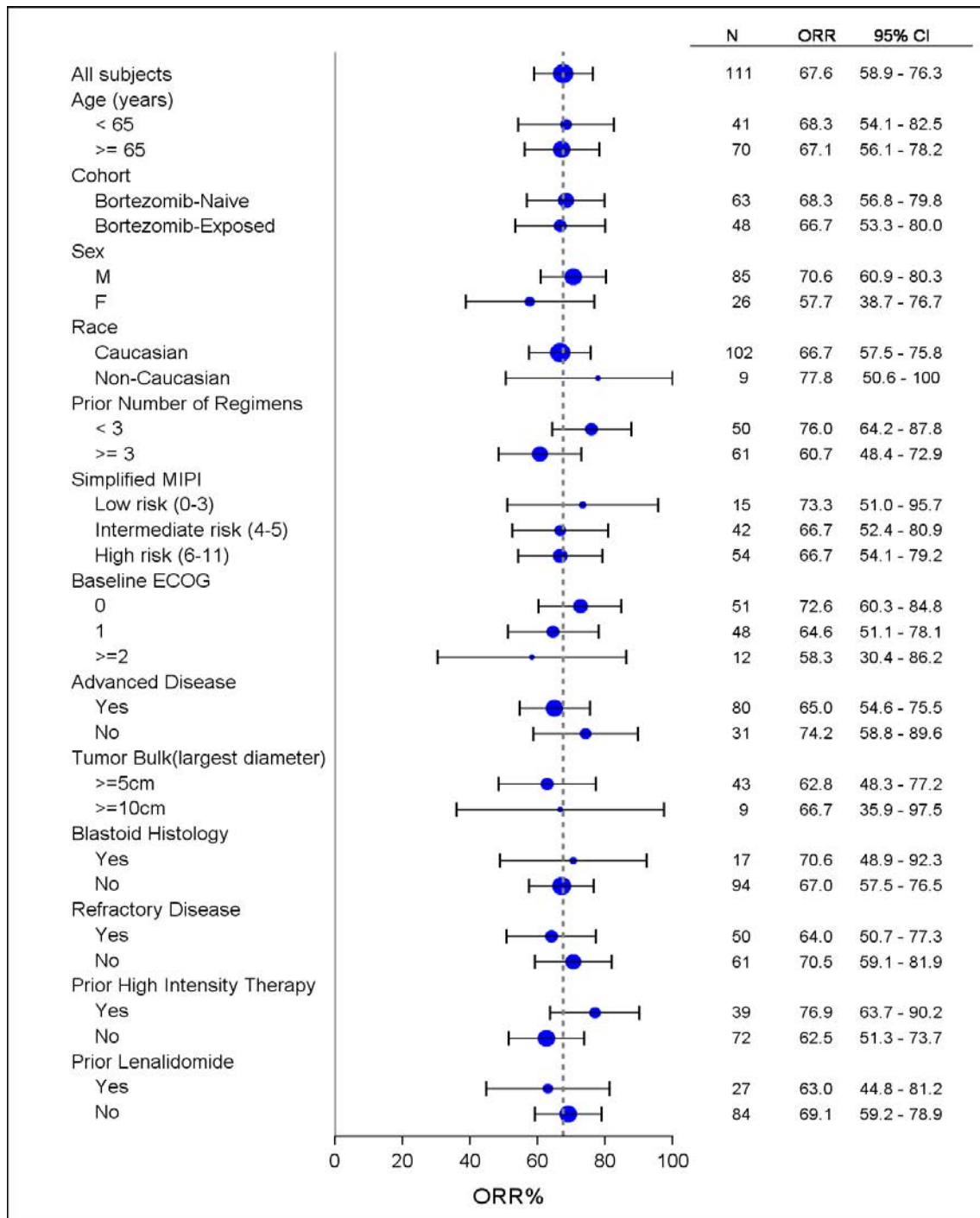
	<b>Total N=111</b>
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9 (1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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)**



### **Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma**

The safety and efficacy of ibrutinib in CLL/SLL in patients who have received at least one prior therapy were demonstrated in one uncontrolled study and one randomised, controlled study.

An open label, multi-centre study (PCYC-1102-CA) included 51 CLL/SLL patients with CLL/SLL who had relapsed or refractory disease and received 420 mg of ibrutinib once daily. Ibrutinib 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 92.2% with a prior nucleoside analog, 98.0% with prior rituximab, 86.3% with a prior alkylating agent, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At study entry, 54.9% of patients had Rai Stage III or IV, 45.1% had bulky disease ( $\geq 5$  cm), 35.3% had del 17p, 31.4% 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 16.4 months, responses to IMBRUVICA for the 51 patients are shown in Table 2.

**Table 2: Overall Response Rate in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 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 <sup>†</sup>
Median Time to Initial Response, months (range)	1.8 (1.4, 12.2)

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

<sup>†</sup> 92.5% of responders were censored (i.e., progression free and alive) with a median follow up of 16.4 months.

The efficacy data were further evaluated using IWCLL criteria by an independent review committee (IRC), demonstrating an ORR of 64.7% (95% CI: 50.1%, 77.6%), all partial responses. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

A randomized, multi-centre, open-label Phase 3 study of ibrutinib versus ofatumumab (PCYC-1112-CA) was conducted in patients with CLL/SLL. Patients (n=391) were randomized 1:1 to receive either ibrutinib 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2000mg). Fifty-seven (n=57) patients randomized to ofatumumab crossed over following progression to receive ibrutinib. 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  $\geq 5$  cm. Thirty-two percent (32%) of patients had deletion 17p and 31% had 11q deletion.

Progression free survival (PFS) as assessed by independent review committee (IRC) according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the ibrutinib arm. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the risk of death for patients in the ibrutinib arm. Efficacy results for Study PCYC-1112-CA are shown in Table 3.

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

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

<sup>a</sup> Median OS not reached for both arms.

<sup>b</sup> Patients randomised to ofatumumab who progressed were censored when starting ibrutinib if applicable.

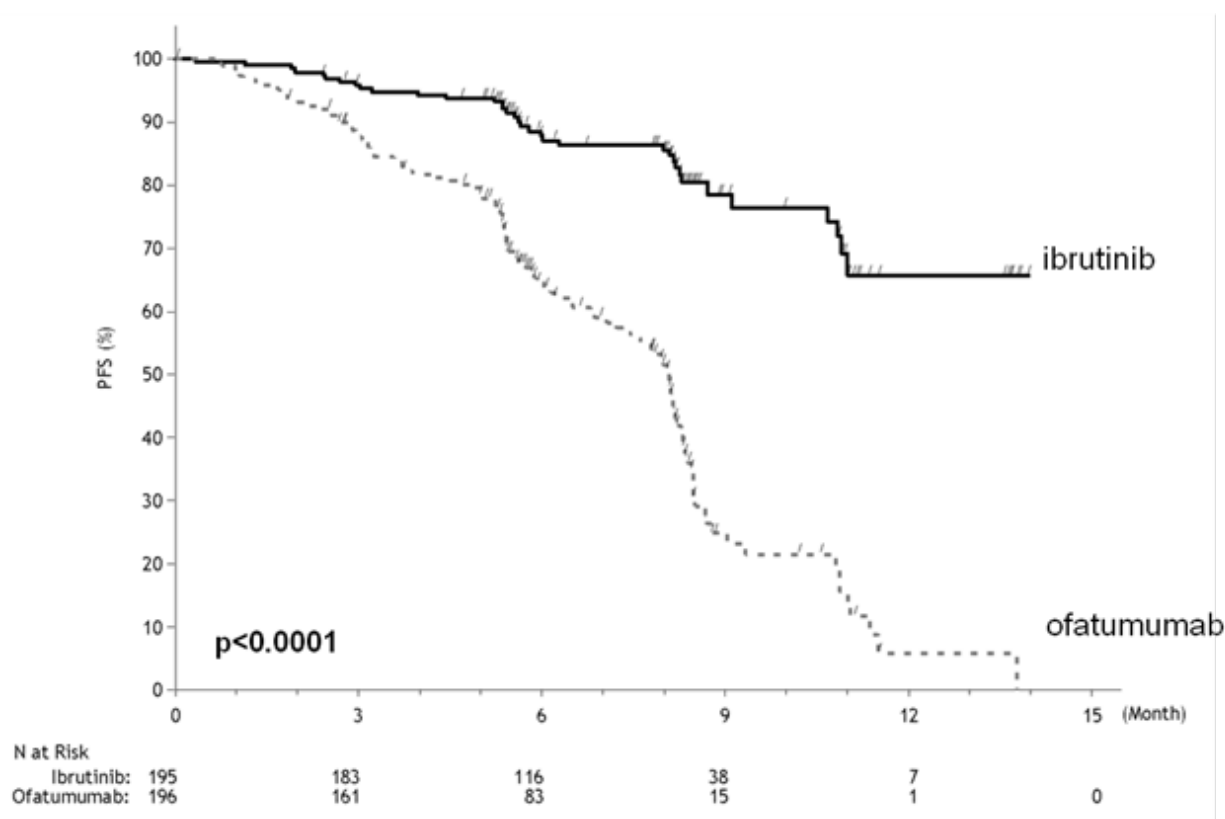
<sup>c</sup> Sensitivity analysis in which crossover patients from the ofatumumab arm were not censored at the date of first dose of ibrutinib.

<sup>d</sup> Per IRC

<sup>e</sup> All PRs achieved.  $p < 0.0001$  for ORR. Repeat CT scans required to confirm response.

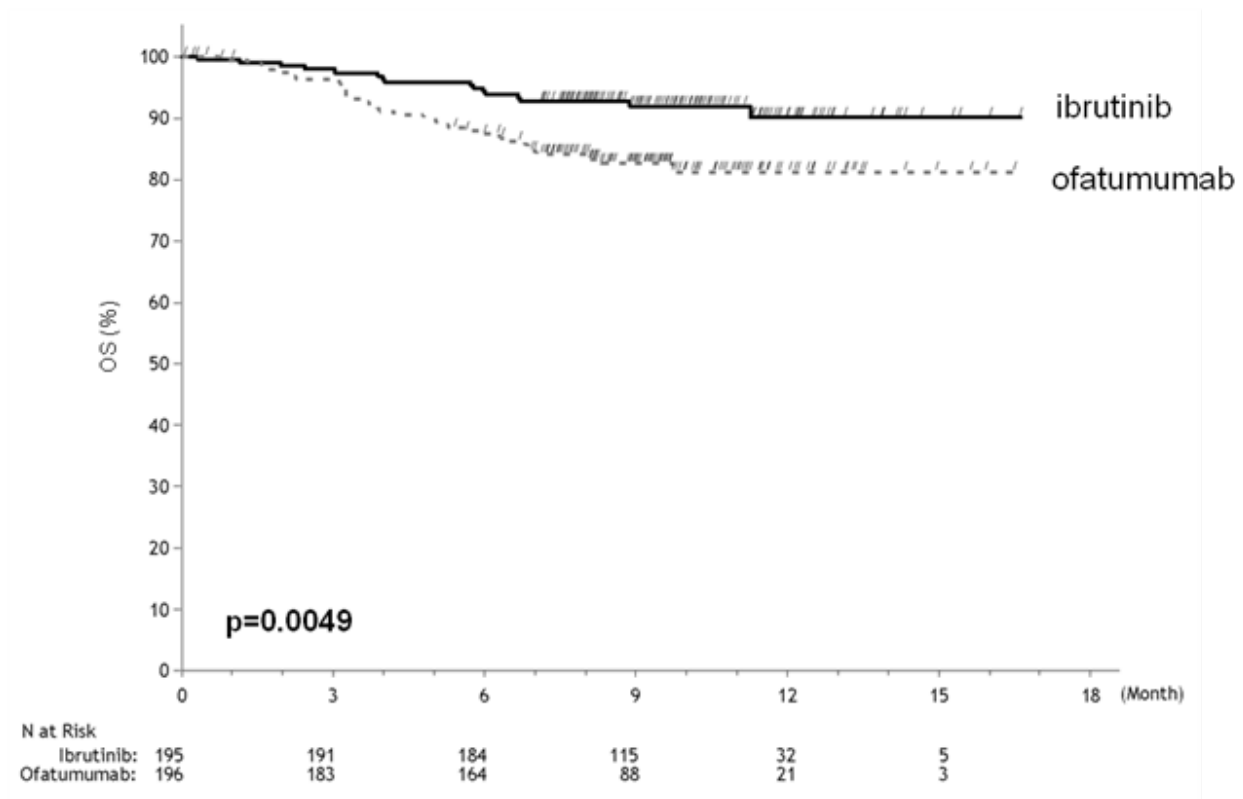
The Kaplan-Meier curves for PFS and OS are shown in Figures 2 and 3, respectively.

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





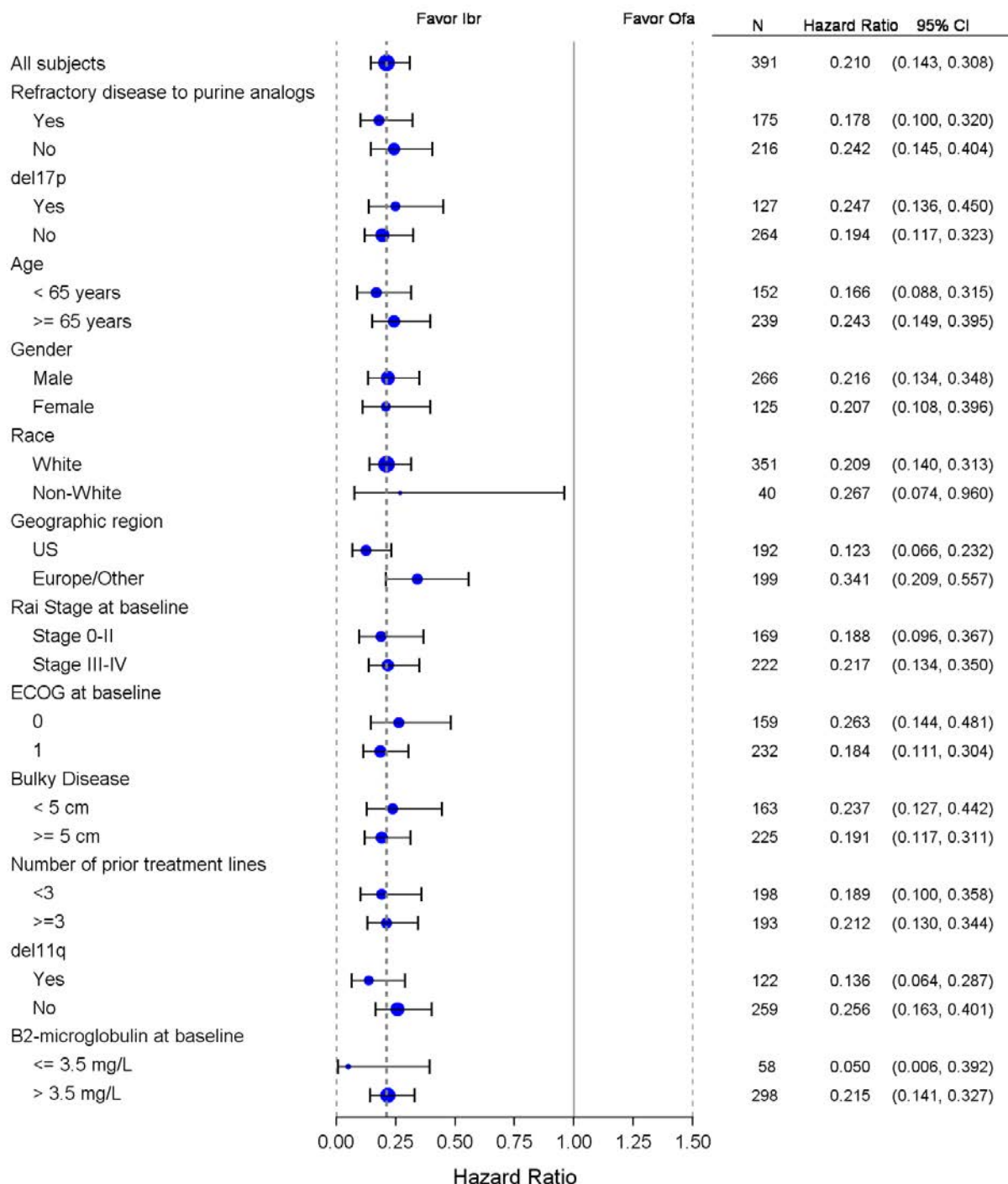
**Figure 3: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA**



The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 4).



**Figure 4: Subgroup Analysis of Progression Free Survival by IRC (Study PCYC-1112-CA; 420 mg)**



## **INDICATIONS**

IMBRUVICA is indicated for the treatment of

- patients with CLL/SLL who have received at least one prior therapy or as first line in patients with CLL with 17p deletion
- patients with MCL who have received at least one prior therapy

## **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.

## **PRECAUTIONS**

### **Bleeding-related events**

There have been reports of haemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor haemorrhagic events such as contusion, epistaxis, and petechiae; and major haemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial haemorrhage, and haematuria.

Patients were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Patients with congenital bleeding diathesis have not been studied.

Ibrutinib should be withheld at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

### **Leukostasis**

There were isolated cases of leukostasis reported in patients treated with ibrutinib. Leukostasis is characterized by abnormal intravascular leukocyte aggregation and clumping, and may cause local hypoxemia and haemorrhage manifesting as headache, blurred vision, transient ischemic attacks, cerebrovascular accidents and dyspnoea. A high number of circulating lymphocytes ( $> 400 \times 10^9/L$ ) may confer increased risk. Consider temporarily withholding ibrutinib. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

### **Infections**

Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalisation and death. Most patients 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.

### **Progressive multifocal leukoencephalopathy (PML)**

Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Patients should be monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. If these occur, ibrutinib should be held pending appropriate investigations.

### **Cytopenias**

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

### **Cardiac events**

Atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms or new onset of dyspnoea 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.

In patients with pre-existing 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, and benefit-risk evaluation dictates the treatment with anticoagulants, patients should be closely monitored.

### **Effects on the QT interval**

A formal QTc study has not been performed. In a phase 2 study, ECG evaluations showed IMBRUVICA produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).

### **Second primary malignancies**

Other malignancies, most frequently skin cancers, have occurred in patients treated with ibrutinib. Monitor regularly for the development of skin cancers.

### **Tumor lysis syndrome**

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

### **Hepatotoxicity**

Severe liver toxicity, such as hepatic failure (Grade 3 and 4 elevations in ALT and AST) have occurred in the post-marketing setting in patients taking ibrutinib. The time to onset was variable (5 days – 3 months after commencing ibrutinib) and monitoring of liver function tests is recommended. These events were very rare and in most cases resolved upon dose modification. Ibrutinib treatment should be interrupted if  $\geq$  Grade 3 liver function abnormalities develop (see Dosage and Administration).

### **Effects on fertility**

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.

Fertility studies with ibrutinib have not been conducted in animals.

### Use in Pregnancy

#### **Category D**

There are no adequate and well controlled studies of ibrutinib in pregnant women. Based on findings in animals, ibrutinib 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 second barrier method. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months 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 foetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown.

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 80 mg/kg/day (approximately 14 times the AUC of ibrutinib and 10 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  $\geq 40$  mg/kg/day (approximately 6 times the AUC of ibrutinib and 4 times the AUC of the dihydrodiol metabolite compared to patients at a dose of 560 mg daily) was associated with decreased maternal and fetal weights and increased skeletal variations (unossified sternebrae).

### Use in Lactation

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.

### Paediatric Use

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

### Genotoxicity

Ibrutinib has no genotoxic properties when tested for mutagenicity in bacteria or clastogenicity in *in vitro* assays (chromosomal aberration in Chinese hamster ovary cells) or *in vivo* (mouse micronucleus test).

### Carcinogenicity

Carcinogenicity studies have not been conducted with ibrutinib.

## **INTERACTIONS WITH OTHER MEDICINES**

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4.

### **Agents that may increase ibrutinib plasma concentrations**

Concomitant use of IMBRUVICA and drugs that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and should be avoided.

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure ( $C_{max}$  and  $AUC_{0-last}$ ) of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was  $\leq 2$ -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 CYP3A4 inhibitors. Clinical safety data in 66 patients treated with moderate

(n=47) or strong CYP3A4 inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone and cobicistat) and moderate inhibitors (e.g., voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. If the benefit clearly outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg or withhold treatment temporarily (for 7 days or less). If a moderate CYP3A4 inhibitor must be used, reduce IMBRUVICA treatment to 140 mg for the duration of the inhibitor use. 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 CYP3A4 (see Dosage and Administration and Pharmacokinetics).

#### *Mild CYP3A4 inhibitors*

Simulations using fasted conditions suggested that the mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by a factor of less than 2-fold. No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed.

#### **Agents that may decrease ibrutinib plasma concentrations**

Administration of IMBRUVICA with strong inducers of CYP3A4 decreases ibrutinib plasma concentrations by approximately 90%. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampicin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A4 induction. If a CYP3A4 inducer must be used, closely monitor patients for lack of efficacy with IMBRUVICA.

As ibrutinib solubility is pH dependent, there is a theoretical risk that medicinal products increasing stomach pH (e.g., proton pump inhibitors) may decrease ibrutinib exposure. This interaction has not been studied in vivo.

#### **Agents that may have their plasma concentrations altered by ibrutinib**

Ibrutinib is a P-gp inhibitor in vitro. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after IMBRUVICA.

There is a risk that ibrutinib may inhibit intestinal CYP3A4 and thereby increase the exposure of CYP3A4 substrates with a large contribution of intestinal CYP3A4 metabolism to its first pass extraction. This interaction has not been studied in vivo and its clinical relevance is currently unknown.

#### **Effect on Ability to Drive or Operate Machinery**

Fatigue, dizziness and asthenia have been reported in some patients taking ibrutinib and should be considered when assessing a patient's ability to drive or operate machinery.

## **ADVERSE EFFECTS**

#### Summary of the safety profile

The safety profile is based on pooled data from 357 patients treated with IMBRUVICA in two phase 2 clinical studies and one randomised phase 3 study. Patients treated for MCL received IMBRUVICA at 560 mg once daily and patients treated for CLL received IMBRUVICA at 420 mg once daily. All patients received IMBRUVICA until disease progression or no longer tolerated.

The most commonly occurring adverse reactions ( $\geq 20\%$ ,) were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia and constipation. The most common grade 3/4 adverse reactions ( $\geq 5\%$ ) were anaemia, neutropenia, pneumonia and thrombocytopenia.

Tabulated list of adverse reactions

Treatment-emergent adverse reactions for MCL or CLL are listed below by system organ class and frequency grouping. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.



**Table 4 Treatment-emergent Adverse drug reactions (ADR) in MCL, CLL patients treated with ibrutinib (N = 357)**

System organ class	Frequency (All grades)	Adverse drug reactions
Infections and infestations	Very common	Pneumonia* Upper respiratory tract infection Sinusitis*
	Common	Sepsis* Urinary tract infection Skin infection*
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia Anaemia
	Common	Febrile neutropenia Leukocytosis Lymphocytosis
	Uncommon	Leukostasis
Metabolism and nutrition disorders	Common	Dehydration Hyperuricaemia
Nervous system disorders	Very common	Dizziness Headache
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage* Bruising* Petechiae
	Common	Subdural haematoma Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation
	Common	Dry mouth
Skin and subcutaneous tissue disorders	Very common	Rash*
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral

\* Includes multiple adverse reaction terms.

#### *Discontinuation and dose reduction due to ADRs*

Of the 357 patients treated with IMBRUVICA for CLL or MCL 6% discontinued treatment primarily due to adverse reactions. These included infections and subdural haematoma. Adverse reactions leading to dose reduction occurred in approximately 8% of patients.

#### *Elderly*

Of the 357 patients treated with IMBRUVICA, 60% were above 65 years of age. Pneumonia, anaemia, dizziness, atrial fibrillation, urinary tract infection, and constipation occurred more frequently among elderly patients treated with IMBRUVICA.

#### **Postmarketing data**

Adverse reactions identified during post-marketing experience with frequency category estimated from spontaneous reporting rates:

System Organ Class: Metabolism and nutrition disorders



Very rare: tumour lysis syndrome

System Organ Class: Skin and subcutaneous tissue disorders

Very rare: Angioedema, erythema, urticaria

System Organ Class: Hepatobiliary disorders

Very rare: Hepatic failure\*; hepatotoxicity

## **DOSAGE AND ADMINISTRATION**

### **Dosage**

IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. IMBRUVICA can be taken with or without food. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville Oranges.

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 (four capsules) once daily.

### **Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL)**

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

### **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 WITH OTHER MEDICINES).

IMBRUVICA therapy should be withheld for any new onset or worsening Grade  $\geq 3$  non-haematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 haematological toxicities. If  $\geq$  Grade 3 elevations in liver function tests occur, with or without a rise in bilirubin, therapy should be withheld.

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, the dose should be reduced by one capsule (140 mg). 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.

<b>Toxicity occurrence</b>	<b>MCL dose modification after recovery</b>	<b>CLL/SLL dose modification after recovery</b>
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 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**

#### *Elderly*

No specific dose adjustment is required for elderly patients (aged  $\geq 65$  years).

#### *Severe cardiac disease*

Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.

#### *Paediatrics (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 ibrutinib clinical studies. 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 (see Pharmacokinetics).

#### *Hepatic impairment*

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT)  $\geq 3 \times$  upper limit of normal (ULN) were excluded from IMBRUVICA clinical studies. In a dedicated hepatic impairment study in non-cancer patients, preliminary data showed an increase in ibrutinib exposure (see Pharmacokinetics). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily (two capsules). For patients with moderate liver impairment, the recommended dose is 140mg daily (one capsule). Monitor patients for signs of ibrutinib 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).

#### *Immunisations*

There is no clinical data on the safety and efficacy of immunisations concomitantly administered with ibrutinib. Immunisations may be less effective in patients on ibrutinib therapy.

#### *Hepatitis B reactivation*

The risk of Hepatitis B reactivation with IMBRUVICA is unknown. Consider screening for hepatitis B prior to commencing IMBRUVICA.

## **OVERDOSAGE**

### **Symptoms and signs**

There are limited data on the effects of IMBRUVICA overdose. Contact the Poisons Information Centre (telephone 131126) for advice on management of 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.

## **PRESENTATION AND STORAGE CONDITIONS**

IMBRUVICA 140 mg ibrutinib capsules are supplied in a white HDPE bottle with a child resistant closure.

Each HDPE bottle with a polypropylene closure contains 90 or 120 hard capsules. Store below 30°C.

## **NAME AND ADDRESS OF SPONSOR**

JANSSEN-CILAG Pty Ltd  
1-5 Khartoum Rd  
Macquarie Park NSW 2113 Australia  
NZ Office: Auckland New Zealand

## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine (Schedule 4)

## **DATE OF FIRST INCLUSION IN THE ARTG**

20 April 2015

## **DATE OF MOST RECENT AMENDMENT**

3 February 2016  
Co-developed with Pharmacyclics