IMBRUVICA®

IBRUTINIB

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Ibrutinib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMBRUVICA capsules contain 140 mg ibrutinib as the active ingredient.

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.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

IMBRUVICA 140 mg capsules are supplied as white opaque capsules. Each white opaque, size 0, hard gelatin capsule is marked with “ibr 140 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

IMBRUVICA is indicated for the treatment of:

- patients with MCL who have received at least one prior therapy
- adult patients with CLL/SLL who have received at least one prior therapy, or adult patients with previously untreated CLL/SLL (see Clinical Trials)
- patients with CLL/SLL with deletion 17p
- adult patients with Waldenstrom’s macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for combination chemo-immunotherapy

4.2 DOSE AND METHOD OF 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 until disease progression or no longer tolerated by the patient.

Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma (CLL/SLL) and Waldenström's Macroglobulinemia (WM)

The recommended dose of IMBRUVICA for CLL/SLL or WM is 420 mg (three capsules) once daily until disease progression or no longer tolerated by the patient.

The recommended dose of IMBRUVICA for CLL/SLL when used in combination with bendamustine and rituximab (BR) (administered every 28 days for up to 6 cycles) is 420 mg (three 140 mg capsules) orally once daily until disease progression or no longer tolerated by the patient. For additional information concerning BR, see the corresponding local BR prescribing information.

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 ≥ 3 non-haematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 haematological toxicities. If ≥ 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.

Toxicity occurrence	MCL dose modification after recovery	CLL/SLL/WM 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 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 ≥ 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 **5.2 PHARMACOKINETIC PROPERTIES**).

Hepatic impairment

Ibrutinib is metabolized in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3 x 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 **5.2 PHARMACOKINETIC PROPERTIES**). 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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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. **In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed (see **5.1 PHARMACODYNAMIC PROPERTIES**)*. Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.

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. Patients with congenital bleeding diathesis have not been studied.

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 x 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, vomiting and jaundice and infections and appropriate anti-infective therapy should be instituted as indicated. **Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections*.

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.

Interstitial Lung Disease (ILD)

Cases of ILD have been reported in patients treated with ibrutinib. 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 events

Atrial fibrillation, atrial flutter and **cases of ventricular tachyarrhythmia, including some fatal events*, have been reported in patients treated with ibrutinib. Cases of **cardiac arrhythmia* have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of **cardiac arrhythmia*.

Periodically monitor all patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms (**chest discomfort, palpitations*, or new onset of dyspnoea, **dizziness, or fainting*) should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed. For **cardiac arrhythmias* which persist, consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

**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 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.

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.

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 ≥ Grade 3 liver function abnormalities develop (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

**Hepatitis B reactivation*

Cases of hepatitis B reactivation have been reported in patients receiving ibrutinib. Hepatitis B virus (HBV) status should be established before initiating treatment with ibrutinib. For patients with hepatitis B serology indicative of prior infection, 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.

Paediatric use

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

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 strong CYP3A inhibitors 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 Cmax 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 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.
**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, cobicistat and posaconazole*) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit clearly outweighs the risk and a strong CYP3A4 inhibitor must be used, see recommended dose modifications in the Table 1.

Moderate and mild CYP3A4 inhibitors
**In patients with B cell malignancies, co administration of CYP3A inhibitors erythromycin and voriconazole increased C_{max} by 3.4-fold and 6.7-fold and increased AUC by 3.0-fold and 5.7-fold, respectively. If a moderate CYP3A4 inhibitor (e.g., fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib,*

*verapamil, amiodarone, dronedarone) is indicated, reduce IMBRUVICA dose as per recommended dose modifications in Table 1. 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 4**.2 DOSE AND METHOD OF ADMINISTRATION** and **5.2 PHARMACOKINETIC PROPERTIES**).*

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.

* ***Table 1 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* • *Posaconazole at doses less than or equal to suspension 200 mg BID*	*140 mg once daily.*
	• *Other strong CYP3A inhibitors* • *Posaconazole at higher doses[b]*	*Avoid concomitant use and consider alternative with less CYP3A inhibitory potential.* *If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA.* *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 **4.2 DOSE AND METHOD OF 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 **4.2 DOSE AND METHOD OF ADMINISTRATION**).*

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

Based on *in vitro* data, ibrutinib is predicted to be a weak OCT2 inhibitor *in vivo.* Ibrutinib is a P-gp and breast cancer resistance protein (BCRP) inhibitor in vitro. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. To minimise 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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 with estimated systemic exposures in female rats approximately 14 times the AUC of ibrutinib and 8 times the AUC of the dihydrodiol metabolite in patients dosed 560 mg ibrutinib daily (exposures in male rats were less than half the exposures in female rats).

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.

Men should be advised not to father a child or donate sperm while receiving IMBRUVICA, and for 3 months following completion of treatment.

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 ≥ 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).

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.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile is based on pooled data from 981 patients with B-cell malignancies treated with IMBRUVICA in three phase 2 clinical studies (PCYC 1102 CA, PCYC 1104 CA and, PCYC 1118E) and four phase 3 studies (PCYC 1112 CA, PCYC 1115 CA, CLL3001 and MCL3001). 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 (≥ 20%) were diarrhoea, musculoskeletal pain, haemorrhage, bruising, rash, nausea, pyrexia and neutropenia. The most common grade 3/4 adverse reactions (≥ 5%) were neutropenia, pneumonia, febrile neutropenia 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Treatment-emergent Adverse drug reactions (ADR) in patients treated with ibrutinib for B-cell malignancies (N = 981)

System organ class	Frequency (All grades)	Adverse drug reactions
Infections and infestations	Very common	Pneumonia* Upper respiratory tract infection Sinusitis* Skin infection*
	Common	Sepsis* Urinary tract infection
Neoplasms benign and malignant (including cysts and polyps)	Common	Non melanoma skin cancer* Basal cell carcinoma Squamous cell carcinoma
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia
	Common	Febrile neutropenia Leukocytosis Lymphocytosis
	Uncommon	Leukostasis syndrome
Metabolism and nutrition disorders	Common	Tumour lysis syndrome Hyponatraemia Hyperuricaemia
Nervous system disorders	Very common	Headache
	Common	Dizziness

Table 2 Treatment-emergent Adverse drug reactions (ADR) in patients treated with ibrutinib for B-cell malignancies (N = 981)

Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage* Bruising*
	Common	Subdural haematoma Petechiae Epistaxis Hypertension*
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation
Skin and subcutaneous tissue disorders	Very common	Rash*
	Common	Erythema Urticaria
	Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms 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 981 patients treated with IMBRUVICA for B-cell malignancies 5% discontinued treatment primarily due to adverse reactions. These included pneumonia, atrial fibrillation and haemorrhage. Adverse reactions leading to dose reduction occurred in approximately 5% of patients.

Elderly

Of the 981 patients treated with IMBRUVICA, 62% were above 65 years of age. Grade 3 or higher pneumonia occurred more frequently (≥5%) among elderly patients treated with IMBRUVICA (13% of patients ≥ 65 years of age versus 7% of patients <65 years of age).

Postmarketing data

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

System Organ Class: Immune system disorders

Uncommon: Interstitial lung disease[*†]

System Organ Class: Metabolism and nutrition disorders

Very rare: [*]*tumour lysis syndrome*

[*]*System Organ Class: Cardiac disorders*

Common: Ventricular tachyarrhythmia[*†]

System Organ Class: Hepatobiliary disorders

Very rare: Hepatic failure[*]; hepatotoxicity

[*]*System Organ Class: Infections and infestations*

Uncommon: Hepatitis B reactivation

System Organ Class: Skin and subcutaneous tissue disorders

Uncommon: Onychoclasis

Rare: Stevens-Johnson syndrome, **Panniculitis**

Very rare: Angioedema, erythema, urticaria

*Includes multiple adverse reaction terms

†Includes events with fatal outcome.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 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.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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., ≥ 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/SLL treated with ibrutinib as a single agent. 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 month of ibrutinib therapy and typically resolves within a median of 8 weeks in patients with MCL and 14 weeks in patients with CLL/SLL (range 0.1 to 104 weeks).

A large increase in the number of circulating lymphocytes (e.g., >400x10^9/L) has been observed in some patients.

Lymphocytosis was not observed in patients with WM treated with IMBRUVICA.

When IMBRUVICA was administered with chemoimmunotherapy, lymphocytosis was infrequent (7% with IMBRUVICA + BR versus 6% with placebo + BR).

***In vitro platelet aggregation**

In an in vitro study (n=32), ibrutinib at therapeutically relevant concentrations demonstrated inhibition of collagen induced platelet aggregation in samples from 4 cohorts of subjects (n=8 in each) with either renal dysfunction, those on warfarin, healthy subjects or healthy subjects on aspirin. 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.

Effects on the QT/QTc interval and cardiac electrophysiology

A randomized, double-blind, placebo- and positive-controlled, single-dose crossover study was performed to evaluate the effects of ibrutinib at supratherapeutic doses of 840 mg and 1680 mg on ECG interval parameters in healthy subjects. The study was early terminated after 20 subjects (out of 52 planned) received 3 out of 4 treatments. Results were based on the 20 treated subjects, 9 of whom received ibrutinib (either 840 or 1680 mg), the negative control (placebo), and the positive control (moxifloxacin). In this study, ibrutinib did not prolong the QTc interval to any clinically relevant extent. 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 dose) that was considered not clinically relevant.

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 (≥ 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 3.

Table 3: Overall Response Rate (ORR) and Duration of Response (DOR) Based on Investigator Assessment in Patients with Mantle Cell Lymphoma

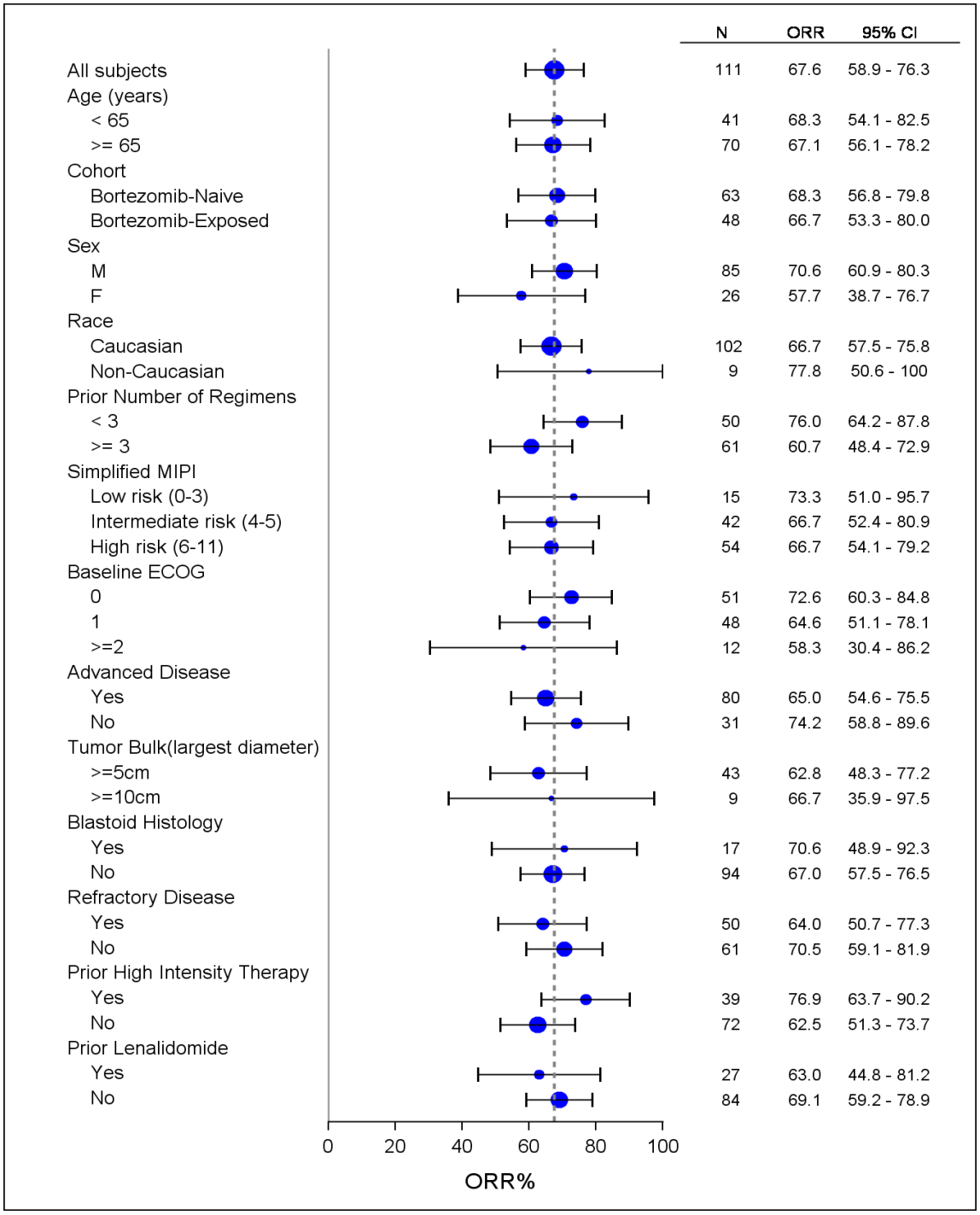
	Total N=111
ORR (%)	67.6
95% CI (%)	(58.0, 76.1)
CR (%)	20.7
PR (%)	46.8
Median DOR (CR+PR) (months)	17.5 (15.8, NR)
Median Time to Initial Response, months (range)	1.9(1.4-13.7)
Median Time to CR, months (range)	5.5 (1.7, 11.5)

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, multicentre 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; 88), 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 International Working Group (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 4 and the Kaplan-Meier curve for PFS Figure 2.

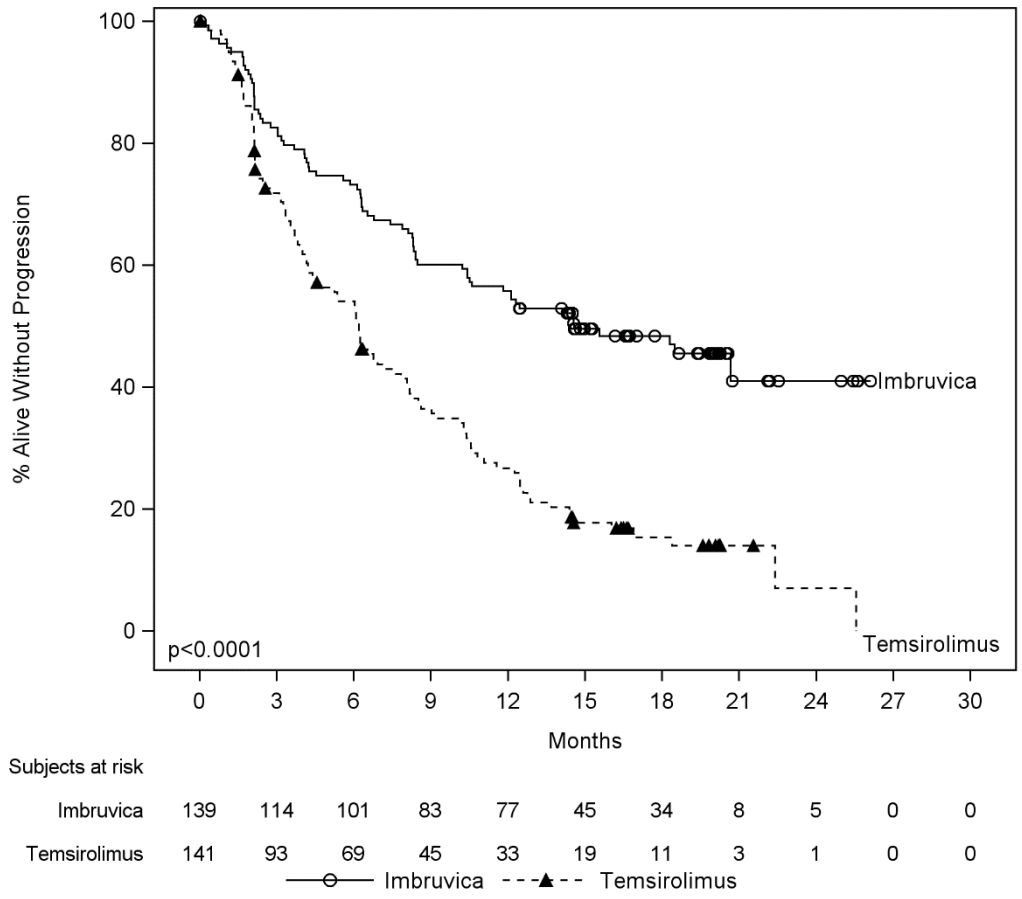
Table 4: Efficacy results in Study MCL3001

Endpoint	**ibrutinib 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	

[a]IRC evaluated

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

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



Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma
The safety and efficacy of ibrutinib in patients with CLL/SLL were demonstrated in one uncontrolled study and two randomised, controlled studies.

Single agent
Patients with treatment naïve CLL/SLL
A randomised, multicentre, open-label Phase 3 study (PCYC-1115-CA) of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL/SLL 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. Patients between 65 and 70 years of age were required to have at least 1 of the following additional comorbidities that could preclude the use of frontline chemoimmunotherapy combination with fludarabine, cyclophosphamide, and rituximab (FCR): Creatinine clearance < 70 mL/min; Platelet count < 100,000 µL or hemoglobin < 10 g/dL; Clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia); ECOG PS score of 1 or 2. Forty-two percent of patients had a baseline ECOG performance status of 0, 49% had an ECOG performance status of 1, and 9 % had an ECOG performance status of 2. The study enrolled 269 patients with CLL or SLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumour ≥ 5 cm, 39% with baseline anaemia, 23% with baseline

thrombocytopenia, 65% had elevated β2 microglobulin > 3500 µg/L, 47% had a CrCL < 60 mL/min, and 20% of patients presented with del11q.

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%). 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 5and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

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

Table 5: Efficacy results in Study PCYC-1115-CA

Endpoint	ibrutinib 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[b] (95% CI)	0.161 (0.091,0.283)	
Overall Response Rate (CR+PR)[a]	82.4%	35.3%
p-value	p<0.0001	
CR/CRi[c]	4.4%	1.5%
Overall Survival[d]		
Number of deaths (%)	3 (2.2)	17 (12.8)
HR (95% CI)	0.163 (0.048, 0.558)	

[a]IRC evaluated; [b]HR = hazard ratio; [c]CRi=complete response with incomplete marrow recovery; [d]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

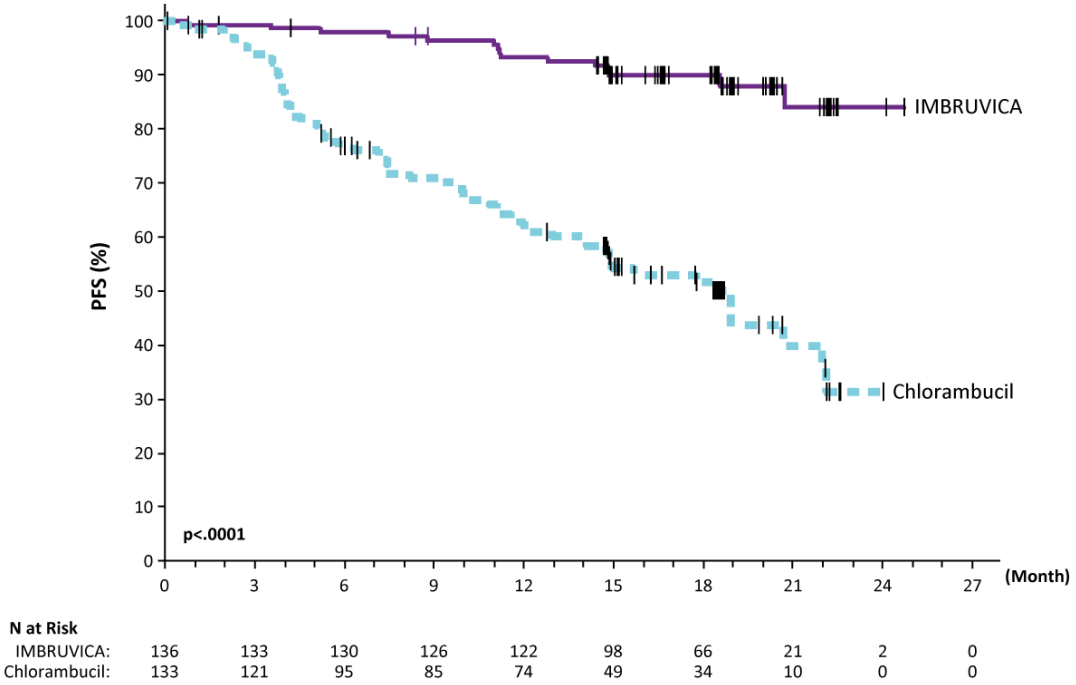
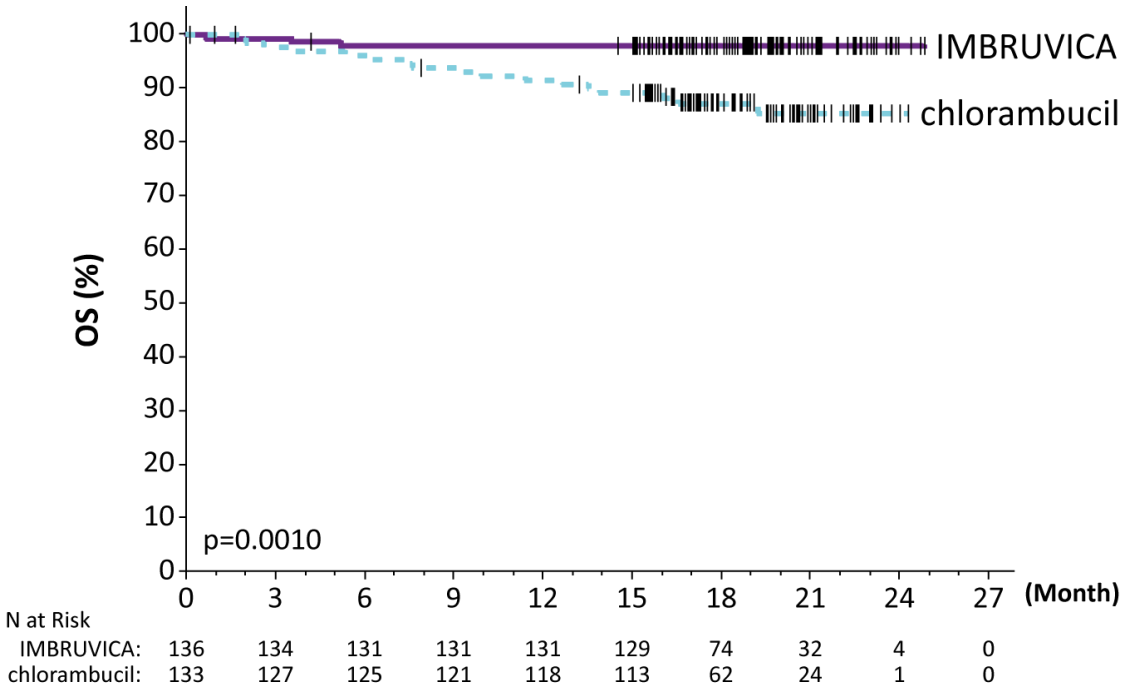


Figure 4: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1115-CA



Patients with CLL/SLL who received at least one prior therapy

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 (≥ 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 6.

Table 6: 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†
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

† 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 ≥ 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 7.

Table 7: 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[a]	HR=0.434 [95% CI: 0.238; 0.789][b] HR=0.387 [95% CI: 0.216 0.695][c]	
Overall Response Rate[d,e] (%)	42.6	4.1
Overall Response Rate including Partial Response with Lymphocytosis (PRL) (%)	62.6	4.1

[a] Median OS not reached for both arms.
[b] Patients randomised 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 ibrutinib.
[d] Per IRC
[e] 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 5 and 6, respectively.

Figure 5: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study PCYC-1112-CA

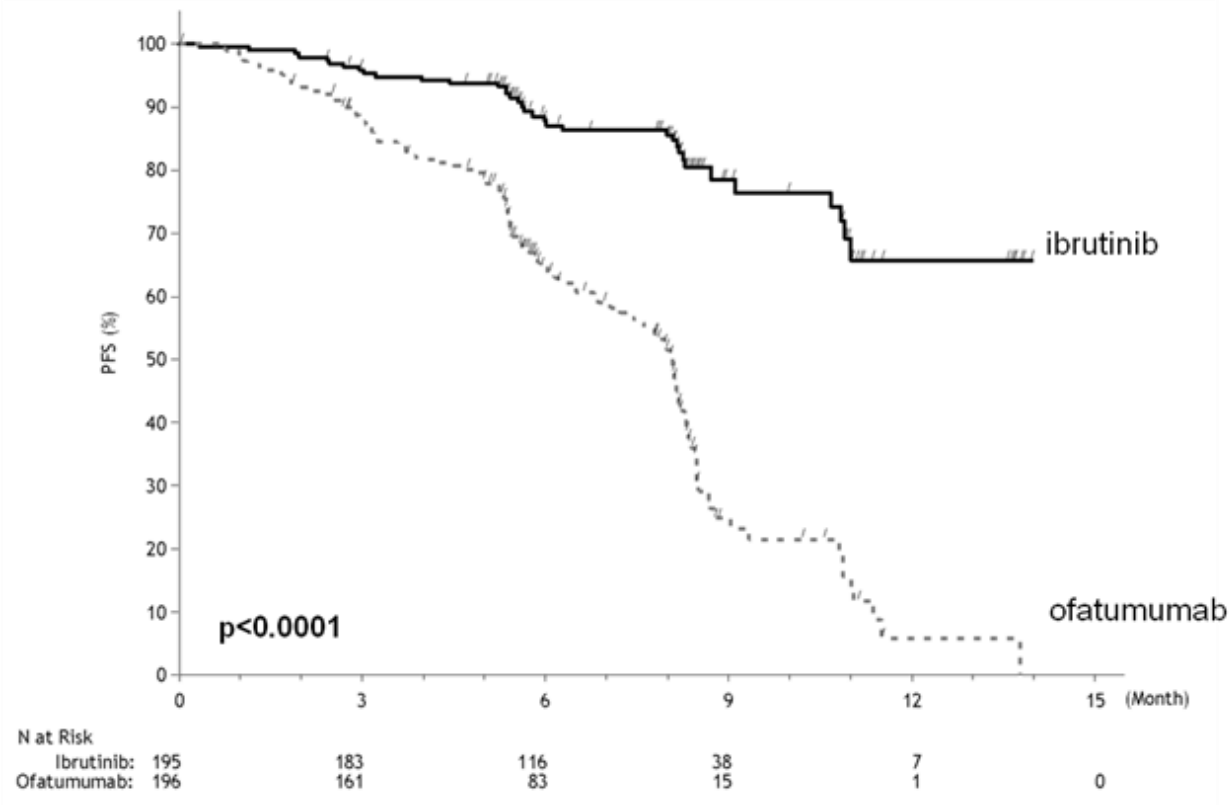
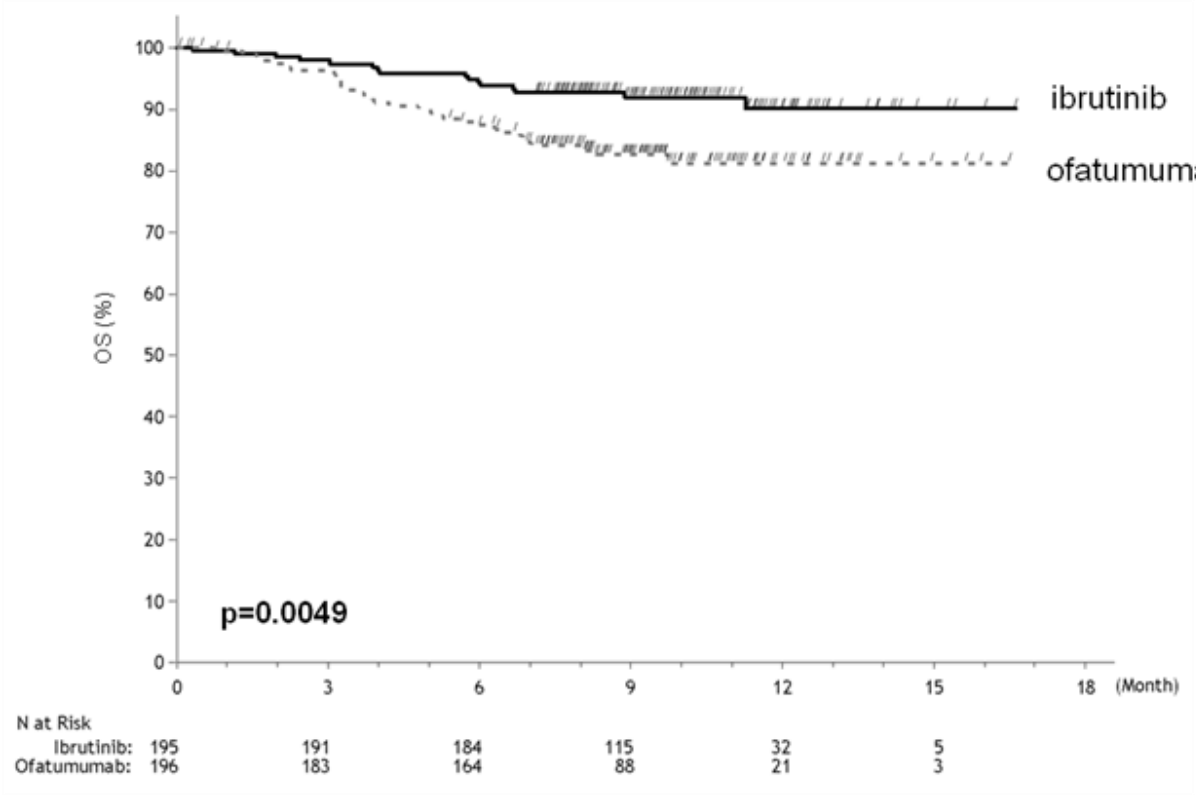
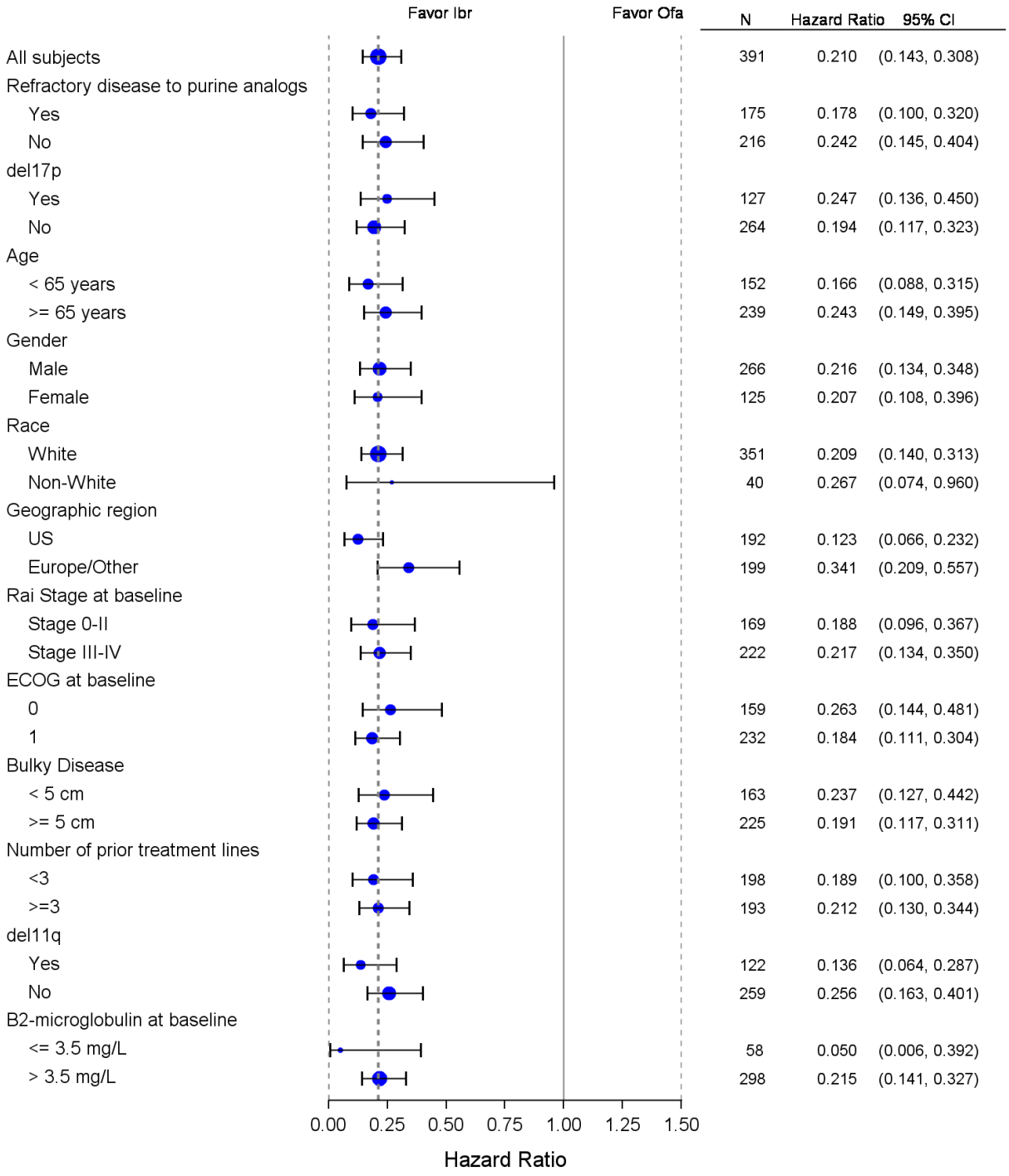


Figure 6: Kaplan-Meier Curve of Overall Survival (ITT Population) in Study PCYC-1112-CA



The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor (Figure 7).

Figure 7: Subgroup Analysis of Progression Free Survival by IRC (Study PCYC-1112-CA; 420 mg)



Combination therapy

The safety and efficacy of IMBRUVICA in patients previously treated for CLL/SLL were further evaluated in a randomized, multicentre, double-blinded Phase 3 study of IMBRUVICA in combination with BR versus placebo + BR (Study CLL3001). Patients (n = 578) were randomized 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2 6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m2 in the first cycle, Day 1, and 500 mg/m2 Cycles 2 through 6, Day 1.

Ninety patients randomized to placebo + BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 5.9 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumour >5 cm, 26% presented with del11q.

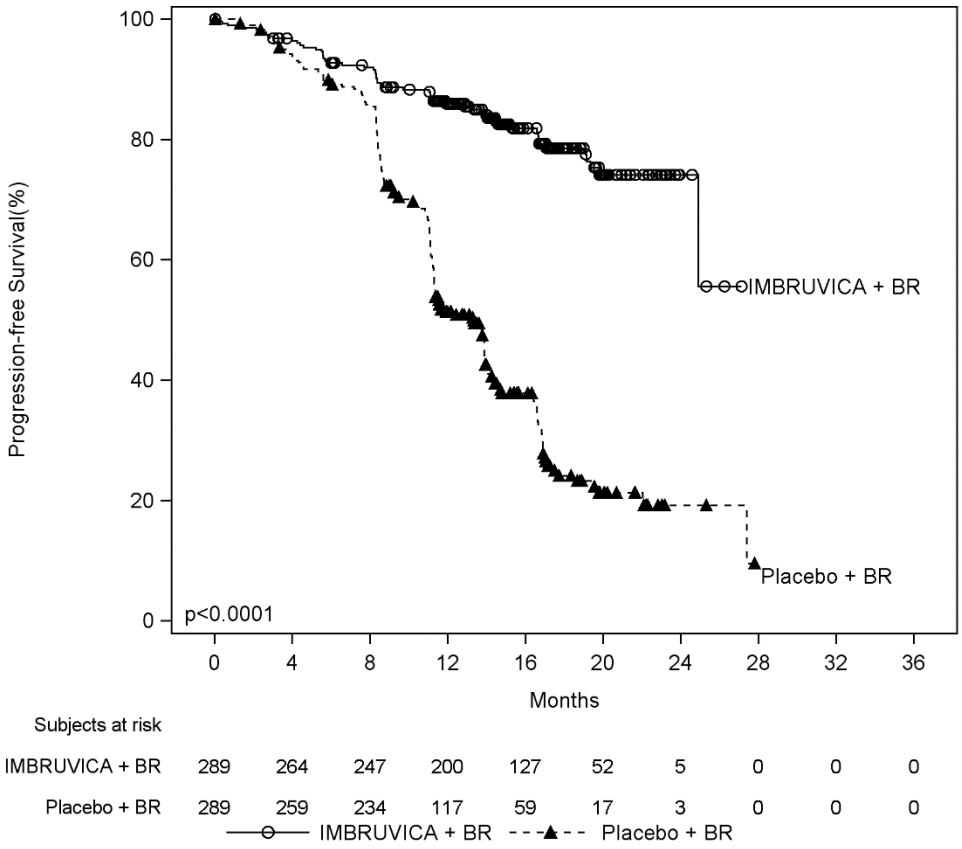
Progression free survival (PFS) as assessed by IRC according to IWCLL criteria indicated an 80% statistically significant reduction in the risk of death or progression. Efficacy results for Study CLL3001 are shown in Table 8 and the Kaplan-Meier curves for PFS are shown in Figure 8.

Table 8: Efficacy results in Study CLL3001

Endpoint	**ibrutinib + BR N=289**	**placebo + BR N=289**
Progression Free Survival		
Number of events (%)	56 (19.4)	183 (63.3
Median (95% CI), months	Not reached	13.3 (11.3,13.9)
HR (95% CI)	0.20 (0.15,0.28)	
Overall Response Rate[a]	82.7%	67.8%
CR/CRi[b]	10.4	2.8
Overall Survival[c]	0.628 (0.385, 1.024)	
Minimal Residual Disease – negative status[d] **(%)**	12.8)	4.8

[a] IRC evaluated, ORR (CR, Cri, nPR, PR)
[b] CRi=complete response with incomplete marrow recovery
[c] Median OS not reached for both arms
[d] MRD was evaluated in patients with suspected complete response; 120 patients for ibrutinib, 57 patients for placebo had MRD samples obtained

Figure 8: Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in Study CLL3001



Waldenström's Macroglobulinemia (WM)

The safety and efficacy of IMBRUVICA in WM (IgM excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multicentre, single arm trial (PCYC-1118E) of 63 previously treated patients. The median age was 63 years (range, 44 to 86 years), 76% were male, and 95% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 74 months, and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, the median serum IgM value was 3.5 g/dL (range, 0.7 to 8.4 g/dL), and 60% of patients were anaemic (haemoglobin ≤11 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR were assessed using criteria adopted from the Third International Workshop of Waldenstrom's Macroglobulinemia. Responses to IMBRUVICA are shown in Table 9.

Table 9: Overall response rate (ORR) and duration of response (DOR) based on investigator assessment in patients with WM

Endpoint	Total (N=63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
CR (%)	0
VGPR (%)	14.3
PR (%)	55.6
MR (%)	17.5
Median DOR months (range)	NR (0.03+, 18.8+)

CI = confidence interval; NR = not reached; MR = minor response; CR = complete response;PR = partial response; VGPR = very good partial response; ORR = MR+PR+VGPR

The median time to response was 1.0 month (range: 0.7-13.4 months).

Efficacy results were also assessed by an IRC demonstrating an ORR of 82.5%, with a 11% VGPR rate and a 51% PR rate.

5.2 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. 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 [^{14}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 in older patients (67 to 81 years), a 14% higher ibrutinib exposure is predicted. Dose adjustment by age is not warranted.

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). Hydration should be maintained and serum creatinine levels monitored periodically. 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.

Co-administration with transporter substrates/inhibitors

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 an *in vitro* inhibitor of OCT2, P gp and BCRP (see **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)**.

5.3 PRECLINICAL SAFETY DATA

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each ibrutinib capsule also contains the following inactive ingredients:

croscarmellose sodium;

magnesium stearate;

microcrystalline cellulose;

sodium lauryl sulfate.

The capsule shell contains:

gelatin;

titanium dioxide

black ink

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

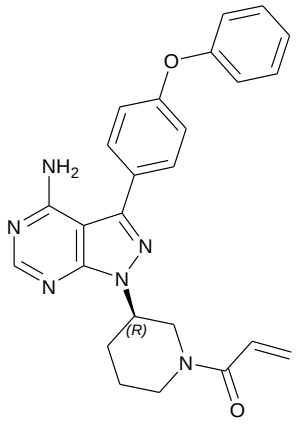
Each HDPE bottle with a polypropylene closure contains 90 or 120 hard capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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.

Molecular formula: $C_{25}H_{24}N_6O_2$ Molecular weight: 440.50

CAS number

936563-96-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Janssen-Cilag Pty Ltd,

1-5 Khartoum Road,

Macquarie Park NSW 2113 Australia

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

20 April 2015

10. DATE OF REVISION

19 July 2018

Co-developed with Pharmacyclics

Summary table of changes

Section changed	Summary of new information
All	1. PI reformat
4.4	2. Revised Precaution subsection Cardiac Effects to add informstion about cardiac arrhythmias
4.5	3. Revised dosage modification advice for use of ibrutinib with strong CYP3A inhibitors
4.8	4. Add new Adverse Effect Panniculitis

Please note change(s) presented as *italicised text in Product Information