เอกสารกำกับยาภาษาอังกฤษ

IMBRUVICA®

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA® 140 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 140 mg of ibrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

White opaque, hard capsule of 22 mm in length, marked with “ibr 140 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

IMBRUVICA as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

4.2 Posology and method of administration

Treatment with this medicinal product should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

Mantle cell lymphoma
The recommended dose for the treatment of MCL is 560 mg (four capsules) once daily.

Chronic lymphocytic leukaemia
The recommended dose for the treatment of CLL, either as a single agent or in combination, is 420 mg (three capsules) once daily (see section 5.1 for details of the combination regimen).

Treatment should continue until disease progression or no longer tolerated by the patient.

Dose adjustments

Moderate and strong CYP3A4 inhibitors increase the exposure of ibrutinib (see sections 4.4 and 4.5).

The IMBRUVICA dose should be lowered to 280 mg once daily (two capsules) when used concomitantly with moderate CYP3A4 inhibitors.

The IMBRUVICA dose should be reduced to 140 mg once daily (one capsule) or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors.

IMBRUVICA therapy should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily 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 the medicinal product.

Recommended dose modifications are described below:

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

Renal impairment
No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. Administer IMBRUVICA to patients with severe renal impairment (< 30 mL/min creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. In a hepatic impairment study, data showed an increase in ibrutinib exposure (see section 5.2). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

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

Paediatric population
The safety and efficacy of IMBRUVICA in children aged 0 to 18 years have not been established. No data are available.

Method of administration
IMBRUVICA should be administered orally once daily with a glass of water approximately at the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville oranges (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 IMBRUVICA, 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 IMBRUVICA 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 IMBRUVICA. Supplements such as fish oil and vitamin E preparations should be avoided. Use of IMBRUVICA in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used.

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

The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

Leukostasis
Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily holding IMBRUVICA. 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 IMBRUVICA. 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. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Cases of Progressive Multifocal Leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioral signs or symptoms. If PML is suspected then appropriate

diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments should be considered.

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

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

Cardiac arrhythmia
Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia have been reported in patients treated with IMBRUVICA. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for cardiac arrhythmia. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, IMBRUVICA should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

In patients with preexisting atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

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

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.

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

Drug-drug interactions
Co-administration of strong or moderate CYP3A4 inhibitors with IMBRUVICA may lead to increased ibrutinib exposure and consequently a higher risk for toxicity. On the contrary, co-administration of CYP3A4 inducers may lead to decreased IMBRUVICA exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of IMBRUVICA with strong CYP3A4 inhibitors and strong or

moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits clearly outweigh the potential risks. Patients should be closely monitored for signs of IMBRUVICA toxicity if a CYP3A4 inhibitor must be used (see sections 4.2 and 4.5). If a CYP3A4 inducer must be used, closely monitor patients for signs of IMBRUVICA lack of efficacy.

Women of childbearing potential
Women of childbearing potential must use a highly effective method of contraception while taking IMBRUVICA (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Ibrutinib is primarily metabolised by cytochrome P450 enzyme 3A4 (CYP3A4).

Agents that may increase ibrutinib plasma concentrations
Concomitant use of IMBRUVICA and medicinal products that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and strong CYP3A4 inhibitors should be avoided.

Strong CYP3A4 inhibitors
Co-administration of ketoconazole, a very strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the strong CYP3A4 inhibitor voriconazole increased C_{max} by 6.7-fold and AUC by 5.7-fold. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodon, cobicistat, voriconazole and posaconazole) should be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg (one capsule) for the duration of the inhibitor use or withhold IMBRUVICA temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Moderate CYP3A4 inhibitors
In patients with B-cell malignancies taking IMBRUVICA with food, co-administration of the CYP3A4 inhibitor erythromycin increased C_{max} by 3.4-fold and AUC by 3.0-fold. If a moderate CYP3A4 inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone and dronedarone) is indicated, reduce IMBRUVICA dose to 280 mg (two capsules) for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

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

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (see section 4.2).

Agents that may decrease ibrutinib plasma concentrations
Administration of IMBRUVICA with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of rifampicin, a strong CYP3A4 inducer, in 18 fasted healthy subjects, decreased exposure (C_{max} and AUC) of ibrutinib by 92 and 90%, respectively. Avoid concomitant use of strong

or moderate CYP3A4 inducers (e.g., carbamazepine, rifampicin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with IMBRUVICA, as efficacy may be reduced. Consider alternative agents with less CYP3A4 induction. If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. A lower C_{max} was observed in fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days (see section 5.2). There is no evidence that the lower C_{max} would have clinical significance, and medicinal products that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical trials.

Agents that may have their plasma concentrations altered by ibrutinib
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, oral 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 in the liver and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

Based on *in vitro* data, ibrutinib is a weak reversible inhibitor towards CYP3A4 at the intestinal level and may therefore increase the exposure to CYP3A4 substrates sensitive to gut CYP3A metabolism. No clinical data are available on this interaction. Caution should be exercised if co-administering ibrutinib with CYP3A4 substrates administered orally with narrow therapeutic range (such as dihydroergotamine, ergotamine, fentanyl, cyclosporine, sirolimus and tacrolimus).

Based on *in vitro* data, ibrutinib is a weak CYP2B6 inducer and may have the potential to affect the expression of other enzymes and transporters regulated via the constitutive androstane receptor (CAR), e.g. CYP2C9, CYP2C19, UGT1A1 and MRP2. The clinical relevance is not known, but the exposure to substrates of CYP2B6 (such as efavirenz and bupropion) and of co-regulated enzymes may be reduced upon co-administration with ibrutinib.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in females
Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment. It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy
IMBRUVICA should not be used during pregnancy. There are no data from the use of IMBRUVICA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding
It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with IMBRUVICA.

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 (Human Equivalent Dose [HED]16 mg/kg/day) (see section 5.3). No human data on the effects of ibrutinib on fertility are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety profile is based on pooled data from 981 patients treated with IMBRUVICA in three phase 2 clinical studies and four randomised phase 3 studies and from post-marketing experience. Patients treated for MCL in clinical studies received IMBRUVICA at 560 mg once daily and patients treated for CLL or WM in clinical studies received IMBRUVICA at 420 mg once daily. All patients in clinical studies received IMBRUVICA until disease progression or no longer tolerated.

The most commonly occurring adverse reactions (≥ 20%) were diarrhoea, neutropenia, haemorrhage (e.g., bruising), musculoskeletal pain, nausea, rash, and pyrexia. The most common grade 3/4 adverse reactions (≥ 5%) were neutropenia, pneumonia, thrombocytopenia, and febrile neutropenia.

Tabulated list of adverse reactions

Adverse reactions in patients treated with ibrutinib for B-cell malignancies and post-marketing adverse reactions 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), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in clinical studies or during post marketing surveillance in patients with B-cell malignancies[†]

System organ class	Frequency (All grades)	Adverse reactions	All Grades (%)	Grade ≥ 3 (%)
Infections and infestations	Very common	Pneumonia*[#]	16	10
		Upper respiratory tract infection	19	1
		Sinusitis*	11	1
		Skin infection*	10	3
	Common	Sepsis*[#]	4	4
		Urinary tract infection	9	2
	Uncommon	Hepatitis B reactivation[@]	<1	<1
Neoplasms benign and malignant (incl cysts and polyps)	Common	Non-melanoma skin cancer*	6	1
		Basal cell carcinoma	3	< 1
		Squamous cell carcinoma	2	< 1
Blood and lymphatic system disorders	Very common	Neutropenia	30	26
		Thrombocytopenia	20	10
	Common	Febrile neutropenia	5	5
		Leukocytosis	2	1
		Lymphocytosis	2	1
	Uncommon	Leukostasis syndrome	< 1	< 1
Immune system disorders	Common	Interstitial lung disease*[,#,a]	2	< 1
Metabolism and nutrition disorders	Common	Tumour lysis syndrome[a]	1	1
		Hyperuricaemia	7	2
Nervous system disorders	Very common	Headache	13	1
	Common	Dizziness	9	0
Eye disorders	Common	Vision blurred	7	0
Cardiac disorders	Common	Atrial fibrillation	6	3
		Ventricular tachyarrhythmia*[b]	1	0

Vascular disorders	Very common	Haemorrhage*[#]	30	1
		Bruising*	22	< 1
	Common	Subdural haematoma[#]	1	1
		Epistaxis	8	< 1
		Petechiae	7	0
		Hypertension*	10	4
Gastrointestinal disorders	Very common	Diarrhoea	41	3
		Vomiting	14	< 1
		Stomatitis*	13	1
		Nausea	27	1
		Constipation	16	< 1
Hepatobiliary disorders	Not known	Hepatic failure*,[a]	Not known	Not known
Skin and subcutaneous tissue disorders	Very common	Rash*	22	2
	Common	Urticaria[a]	1	< 1
		Erythema[a]	2	0
		Onychoclasis[a]	2	0
	Uncommon	Angioedema[a]	< 1	< 1
	Not known	Stevens-Johnson syndrome[a]	Not known	Not known
Musculoskeletal and connective tissue disorders	Very common	Arthralgia	12	1
		Muscle spasms	14	< 1
		Musculoskeletal pain*	28	3
General disorders and administration site conditions	Very common	Pyrexia	20	2
		Oedema peripheral	14	1

† Frequencies are rounded to the nearest integer.

* Includes multiple adverse reaction terms.

Includes events with fatal outcome.

@ Lower level term (LLT) used for selection.

a Spontaneous reports from post-marketing experience.

b Frequency calculated from monotherapy clinical studies.

Discontinuation and dose reduction due to adverse drug reactions
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 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently among elderly patients treated with IMBRUVICA (13% of patients age ≥ 65 versus 7% of patients < 65 years of age).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system.

4.9 Overdose

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 (1,400 mg/day). In a separate study, one healthy subject who received a dose of 1,680 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 dose should be closely monitored and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important 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. 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 effectively inhibits malignant 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 an absolute count > 5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in about three fourths of patients with CLL treated with IMBRUVICA. This effect has also been observed in about one third of patients with relapsed or refractory MCL treated with IMBRUVICA. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of IMBRUVICA therapy and typically resolves within a median of 8.0 weeks in patients with MCL and 14 weeks in patients with CLL. A large increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in some patients.

Lymphocytosis was not observed in patients with Waldenström's macroglobulinaemia (WM) treated with IMBRUVICA.

In vitro platelet aggregation
In an *in vitro* study, ibrutinib demonstrated inhibition of collagen-induced platelet aggregation. Ibrutinib did not show meaningful inhibition of platelet aggregation using other agonists of platelet aggregation.

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

Clinical efficacy and safety

Mantle cell lymphoma
The safety and efficacy of IMBRUVICA in patients with relapsed or refractory MCL were evaluated in a single open-label, multi-center phase 2 study (PCYC-1104-CA) of 111 patients. The median age was 68 years (range: 40 to 84 years), 77% were male and 92% were Caucasian. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater were excluded from the study. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range: 1 to 5 treatments), including 35% with prior high-dose chemotherapy, 43% with prior bortezomib, 24% with prior lenalidomide, and 11% with prior autologous or allogeneic stem cell

transplant. At baseline, 39% of patients had bulky disease (≥ 5 cm), 49% had high-risk score by Simplified MCL International Prognostic Index (MIPI), and 72% had advanced disease (extranodal and/or bone marrow involvement) at screening.

IMBRUVICA was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. 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 2.

Table 2: Overall response rate (ORR) and duration of response (DOR) in patients with relapsed or refractory MCL (Study PCYC-1104-CA)

	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% complete response (CR) rate and a 48% partial response (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/prognostic factors, bulky disease, gender or age.

The safety and efficacy of IMBRUVICA were demonstrated in a randomised phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients were randomised 1:1 to receive either IMBRUVICA orally at 560 mg once daily for 21 days 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 years), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥ 5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening.

Progession-free survival (PFS) was assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria. Efficacy results for Study MCL3001 are shown in Table 3 and the Kaplan-Meier curve for PFS in Figure 1.

Table 3: Efficacy Results in patients with relapsed or refractory MCL (Study MCL3001)

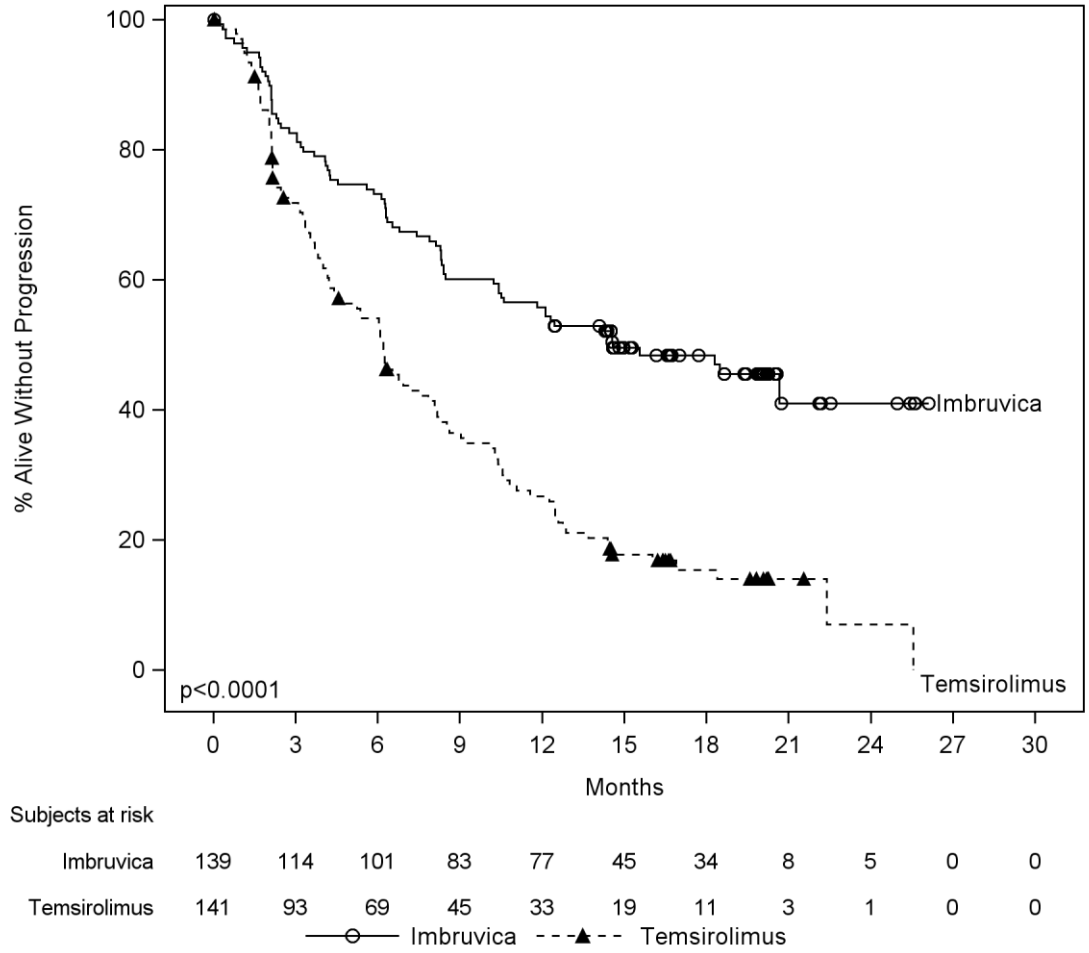
Endpoint	**IMBRUVICA N = 139**	**Temsirolimus N = 141**
Progression-Free Survival[a]		
Median Progression-Free Survival (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR = 0.43 [95% CI: 0.32, 0.58]	
Overall Response Rate (%)	71.9	40.4
p-value	p < 0.0001	

NE = not estimable; HR = hazard ratio; CI = confidence interval

[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 1: Kaplan-Meier curve of progression-free survival (ITT Population) in Study MCL3001



Chronic lymphocytic leukaemia

Patients previously untreated for CLL

A randomised, multicenter, open-label phase 3 study (PCYC-1115-CA) of IMBRUVICA versus chlorambucil was conducted in patients with treatment-naïve CLL who were 65 years of age or older. Patients between 65 and 70 years of age were required to have at least one comorbidity that precluded the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab. Patients (n = 269) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on days 1 and 15 of each 28-day cycle for a maximum of 12 cycles, with an allowance for intrapatient dose increases up to 0.8 mg/kg based on tolerability. After confirmed disease progression, patients on chlorambucil were able to crossover to ibrutinib.

The median age was 73 years (range, 65 to 90 years), 63% were male, and 91% were Caucasian. Ninety one percent of patients had a baseline ECOG performance status of 0 or 1 and 9% had an ECOG performance status of 2. The study enrolled 269 patients with CLL. At baseline, 45% had advanced clinical stage (Rai Stage III or IV), 35% of patients had at least one tumor ≥ 5 cm, 39% with baseline anemia, 23% with baseline thrombocytopenia, 65% had elevated β2 microglobulin > 3500 mcg/L, 47% had a CrCL < 60 ml/min, and 20% of patients presented with del11q.

Progression free survival (PFS) as assessed by IRC according to International Workshop on CLL (IWCLL) criteria indicated an 84% statistically significant reduction in the risk of death or progression

in the IMBRUVICA arm. Efficacy results for Study PCYC-1115-CA are shown in Table 4 and the Kaplan-Meier curves for PFS and OS are shown in Figures 2 and 3, respectively.

There was a statistically significant sustained platelet or hemoglobin improvement in the ITT population in favor of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained hematologic improvement was: platelets 77.1% versus 42.9%; hemoglobin 84.3% versus 45.5% for ibrutinib and chlorambucil respectively.

Table 4: Efficacy results in Study PCYC-1115-CA

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

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

[a] IRC evaluated, median follow--up 18.4 months.

[b] Median OS not reached for both arms. p < 0.005 for OS

Figure 2: Kaplan-Meier curve of progression-free survival (ITT Population) in Study PCYC-1115-CA

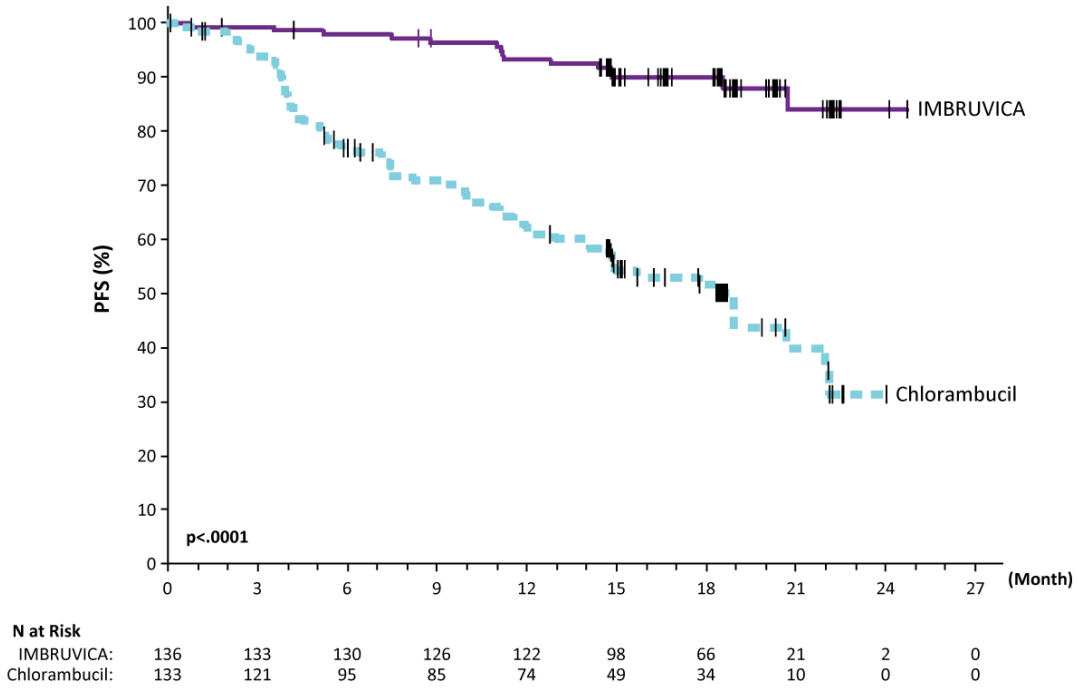
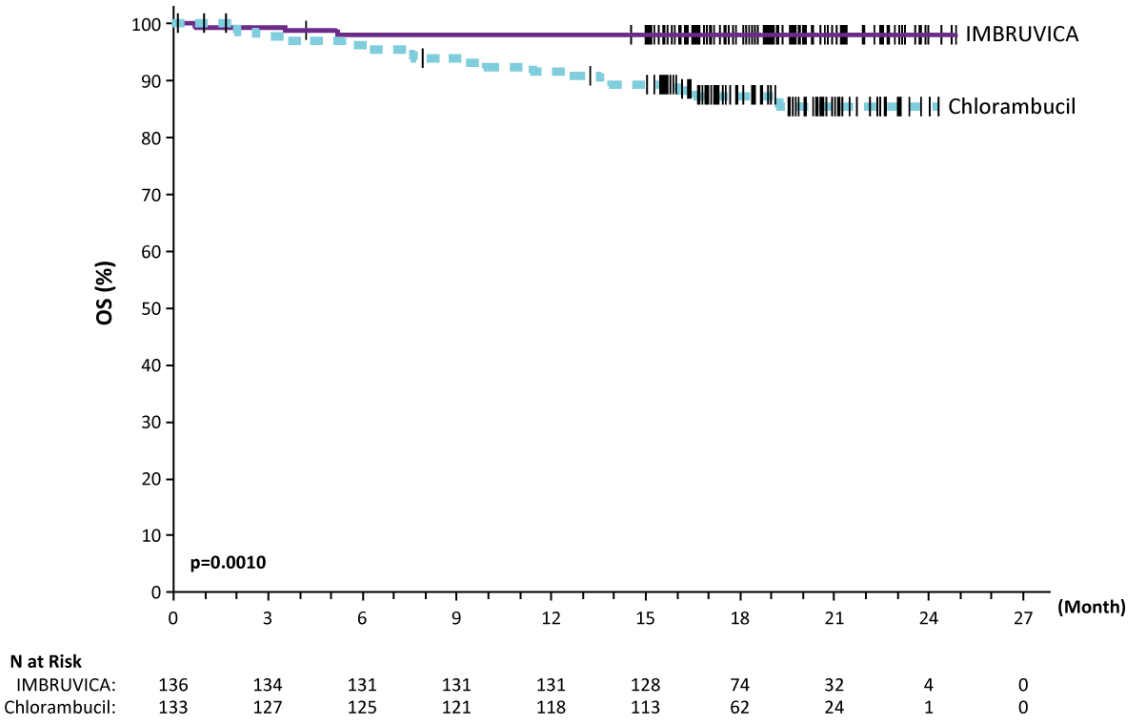


Figure 3: Kaplan-Meier curve of overall survival (ITT Population) in Study PCYC-1115-CA



Patients with CLL who received at least one prior therapy
The safety and efficacy of IMBRUVICA in patients with CLL were demonstrated in one uncontrolled study and one randomised, controlled study. The open-label, multi-center study (PCYC-1102-CA) included 51 patients with relapsed or refractory CLL, who received 420 mg once daily. IMBRUVICA was administered until disease progression or unacceptable toxicity. The median age was 68 years (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 alkylator, 39.2% with prior bendamustine and 19.6% with prior ofatumumab. At baseline, 39.2% of patients had Rai Stage IV, 45.1% had bulky disease (≥ 5 cm), 35.3% had deletion 17p and 31.4% had deletion 11q.

ORR was assessed according to the 2008 IWCLL criteria by investigators and IRC. At a median duration follow up of 16.4 months, the ORR by IRC for the 51 relapsed or refractory patients was 64.7% (95% CI: 50.1%; 77.6%), all PRs. The ORR including PR with lymphocytosis was 70.6%. Median time to response was 1.9 months. The DOR ranged from 3.9 to 24.2+ months. The median DOR was not reached.

A randomised, multi-center, open-label phase 3 study of IMBRUVICA versus ofatumumab (PCYC-1112-CA) was conducted in patients with relapsed or refractory CLL. Patients (n = 391) were randomised 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity, or ofatumumab for up to 12 doses (300/2,000 mg). Fifty-seven patients randomised to ofatumumab crossed over following progression to receive IMBRUVICA. The median age was 67 years (range: 30 to 88 years), 68% were male, and 90% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 91 months and the median number of prior treatments was 2 (range: 1 to 13 treatments). At baseline, 58% of patients had at least one tumour ≥5 cm. Thirty-two percent of patients had deletion 17p and 31% had 11q deletion.

Progression free survival (PFS) as assessed by an IRC according to IWCLL criteria indicated a 78% statistically significant reduction in the risk of death or progression for patients in the IMBRUVICA arm. Analysis of overall survival (OS) demonstrated a 57% statistically significant reduction in the

risk of death for patients in the IMBRUVICA arm. Efficacy results for Study PCYC-1112-CA are shown in Table 5.

Table 5: Efficacy results in patients with chronic lymphocytic leukaemia (Study PCYC-1112-CA)

Endpoint	**IMBRUVICA 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 PR with lymphocytosis[d] (%)	62.6	4.1

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

[a] Median OS not reached for both arms. $p < 0.005$ for OS.

[b] Patients randomised to ofatumumab were censored when starting IMBRUVICA if applicable.

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

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

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

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

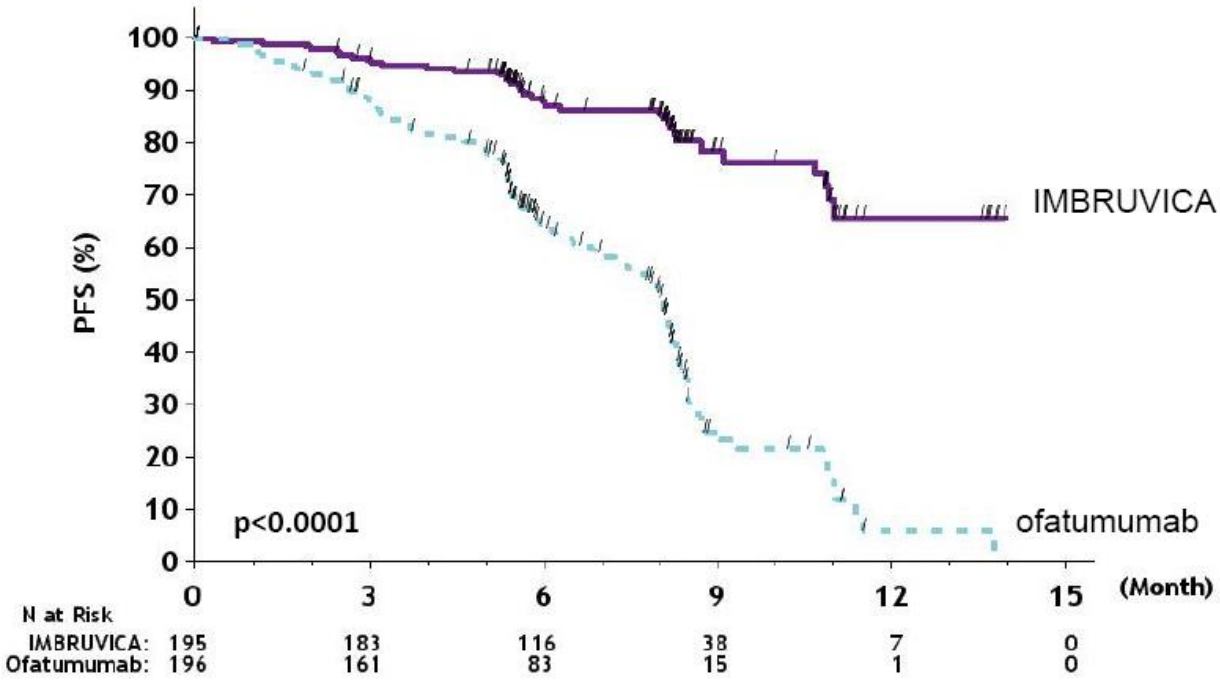
Table 6: Subgroup analysis of progression free survival (Study PCYC-1112-CA)

	N	**Hazard Ratio**	**95% CI**
All subjects	391	0.210	(0.143; 0.308)
Del17P			
Yes	127	0.247	(0.136; 0.450)
No	264	0.194	(0.117; 0.323)
Refractory disease to purine analog			
Yes	175	0.178	(0.100; 0.320)
No	216	0.242	(0.145; 0.404)
Age			
< 65	152	0.166	(0.088; 0.315)
≥ 65	239	0.243	(0.149; 0.395)
Number of prior lines			
< 3	198	0.189	(0.100; 0.358)
≥ 3	193	0.212	(0.130; 0.344)
Bulky disease			
< 5 cm	163	0.237	(0.127; 0.442)
≥ 5 cm	225	0.191	(0.117; 0.311)

Hazard ratio based on non-stratified analysis

The Kaplan-Meier curve for PFS is shown in Figure 4.

Figure 4: Kaplan-Meier curve of progression-free survival (ITT Population) in Study PCYC-1112- CA



Combination therapy

The safety and efficacy of IMBRUVICA in patients previously treated for CLL were further evaluated in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with BR versus placebo + BR (Study CLL3001). Patients (n = 578) were randomised 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/m^2 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/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomised 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 6 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% had del11q.

Progression free survival (PFS) was assessed by IRC according to IWCLL criteria. Efficacy results for Study CLL3001 are shown in Table 7.

Table 7: Efficacy Results in patients with chronic lymphocytic leukaemia (Study CLL3001)

Endpoint	IMBRUVICA + BR N = 289	Placebo + BR N = 289
Progression Free Survival[a]		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR = 0.203 [95% CI: 0.150, 0.276]	
Overall Response Rate[b] %	82.7	67.8
Overall Survival (OS)[c]	HR = 0.628 [95% CI: 0.385, 1.024]	

CI = confidence interval; HR = hazard ratio;

[a] IRC evaluated.

[b] IRC evaluated, ORR (complete response, complete response with incomplete marrow recovery, nodular partial response, partial response).

[c] Median OS not reached for both arms.

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 of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Ibrutinib has a pH dependent solubility, with lower solubility at higher pH. In fasted healthy subjects administered a single 560 mg dose of ibrutinib after taking omeprazole at 40 mg once daily for 5 days, compared to ibrutinib alone, geometric mean ratios (90% CI) were 83% (68-102%), 92% (78-110%), and 38% (26-53%) for AUC_{0-24}, AUC_{last}, and C_{max}, respectively.

Distribution
Reversible binding of ibrutinib to human plasma protein *in vitro* was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_{d, ss}/F$) was approximately 10,000 L.

Metabolism
Ibrutinib is metabolised primarily by CYP3A4 to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal.

Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination
Apparent clearance (CL/F) is approximately 1,000 L/h. The half-life of ibrutinib is 4 to 13 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 < 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine.

Special populations

Elderly
Population pharmacokinetics indicated that age does not significantly influence ibrutinib clearance from the circulation.

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

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

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.

Renal impairment
Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis (see section 4.2).

Hepatic impairment
Ibrutinib is metabolised in the liver. A hepatic impairment trial was performed in non-cancer subjects administered a single dose of 140 mg of medicinal product under fasting conditions. The effect of impaired liver function varied substantially between individuals, but on average a 2.7-, 8.2-, and 9.8-fold increase in ibrutinib exposure (AUC_{last}) was observed in subjects with mild (n = 6, Child-Pugh class A), moderate (n = 10, Child-Pugh class B) and severe (n = 8, Child-Pugh class C) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure ($AUC_{unbound, last}$) is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively (see section 4.2).

Co-administration with CYP substrates
In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and intestinal (but not hepatic) CYP3A4 and does not display clinically relevant time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. The dihydrodiol metabolite is at most a weak inducer of CYP450 isoenzymes *in vitro*. Although ibrutinib is a sensitive CYP3A4 substrate, it does not have a clinically relevant effect on its own exposure.

Co-administration with transport 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 P-gp and BCRP (see section 4.5).

5.3 Preclinical safety data

The following adverse effects were seen in studies of 13-weeks duration in rats and dogs. Ibrutinib was found to induce gastrointestinal effects (soft faeces/diarrhoea and/or inflammation) and lymphoid depletion in rats and dogs with a No Observed Adverse Effect Level (NOAEL) of 30 mg/kg/day in both species. Based on mean exposure (AUC) at the 560 mg/day clinical dose, AUC ratios were 2.6 and 21 at the NOAEL in male and female rats, and 0.4 and 1.8 at the NOAEL in male and female dogs, respectively. Lowest Observed Effect Level (LOEL) (60 mg/kg/day) margins in the dog are 3.6-fold (males) and 2.3-fold (females). In rats, moderate pancreatic acinar cell atrophy (considered adverse) was observed at doses of ≥ 100 mg/kg in male rats (AUC exposure margin of 2.6-fold) and not observed in females at doses up to 300 mg/kg/day (AUC exposure margin of 21.3-fold). Mildly decreased trabecular and cortical bone was seen in female rats administered ≥ 100 mg/kg/day (AUC exposure margin of 20.3-fold). All gastrointestinal, lymphoid and bone findings recovered following recovery periods of 6-13 weeks. Pancreatic findings partially recovered during comparable reversal periods.

Juvenile toxicity studies have not been conducted.

Carcinogenicity/genotoxicity
Carcinogenicity studies have not been conducted with ibrutinib.
Ibrutinib has no genotoxic properties when tested in bacteria, mammalian cells or in mice.

Reproductive toxicity
In pregnant rats, ibrutinib at a dose of 80 mg/kg/day was associated with increased post-implantation loss and increased visceral (heart and major vessels) malformations and skeletal variations with an exposure margin 14 times the AUC found in patients at a daily dose of 560 mg. At a dose of ≥ 40 mg/kg/day, ibrutinib was associated with decreased foetal weights (AUC ratio of ≥ 5.6 as compared to daily dose of 560 mg in patients). Consequently the foetal NOAEL was 10 mg/kg/day (approximately 1.3 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post-implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day). Consequently the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily) (see section 4.6).

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 (Human Equivalent Dose [HED]16 mg/kg/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
croscarmellose sodium
magnesium stearate
microcrystalline cellulose
sodium laurilsulfate

Capsule shell
gelatin
titanium dioxide (E171)

Printing ink
shellac
iron oxide black (E172)
propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

See expiry date on the outer pack.

6.4 Special precautions for storage

Do not store above 30°C. This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a child-resistant polypropylene closure.

Each carton contains one bottle of either 90 or 120 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufactured by	Market Authorization Number	Date of Authorization
Catalent CTS, LLC. Kansas City, MO 64137, USA	1C 74/60 (NC)	2 November 2017
Cilag AG CH-8200 Schaffhausen, Switzerland	1C 73/60 (NC)	2 November 2017

DATE OF REVISION OF THE TEXT

28 September 2017

WARNING

This medicinal product may cause serious harm. It must be used only under physician's supervision.

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