

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström’s macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

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 and Waldenström’s macroglobulinaemia

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).

The recommended dose for the treatment of WM is 420 mg (three capsules) once daily.

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 140 mg once daily (one capsule) 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/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 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. Patients with congenital bleeding diathesis have not been studied.

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.

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 cyto-reduction 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.

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 or moderate CYP3A4 inhibitors/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 should be avoided.

Strong CYP3A4 inhibitors

Co-administration of ketoconazole, a 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. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodon and cobicistat) 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) or withhold treatment 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

Simulations using fasted conditions suggested that moderate CYP3A4 inhibitors, diltiazem, erythromycin and voriconazole, may increase the AUC of ibrutinib 5-9 fold. Moderate inhibitors (e.g., voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. If a moderate CYP3A4 inhibitor must be used, reduce IMBRUVICA treatment to 140 mg (one capsule) 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 clinically relevant 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 ($\geq 20\%$) were diarrhoea, neutropenia, haemorrhage (e.g., bruising), musculoskeletal pain, nausea, rash, and pyrexia. The most common grade 3/4 adverse reactions ($\geq 5\%$) 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ 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
		Onychoclasia ^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** listed in [Appendix V](#).

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., $\geq 50\%$ increase from baseline and an absolute count $> 5,000/\text{mcL}$), 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., $> 400,000/\text{mcL}$) has been observed in some patients.

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

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.

Progression-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)

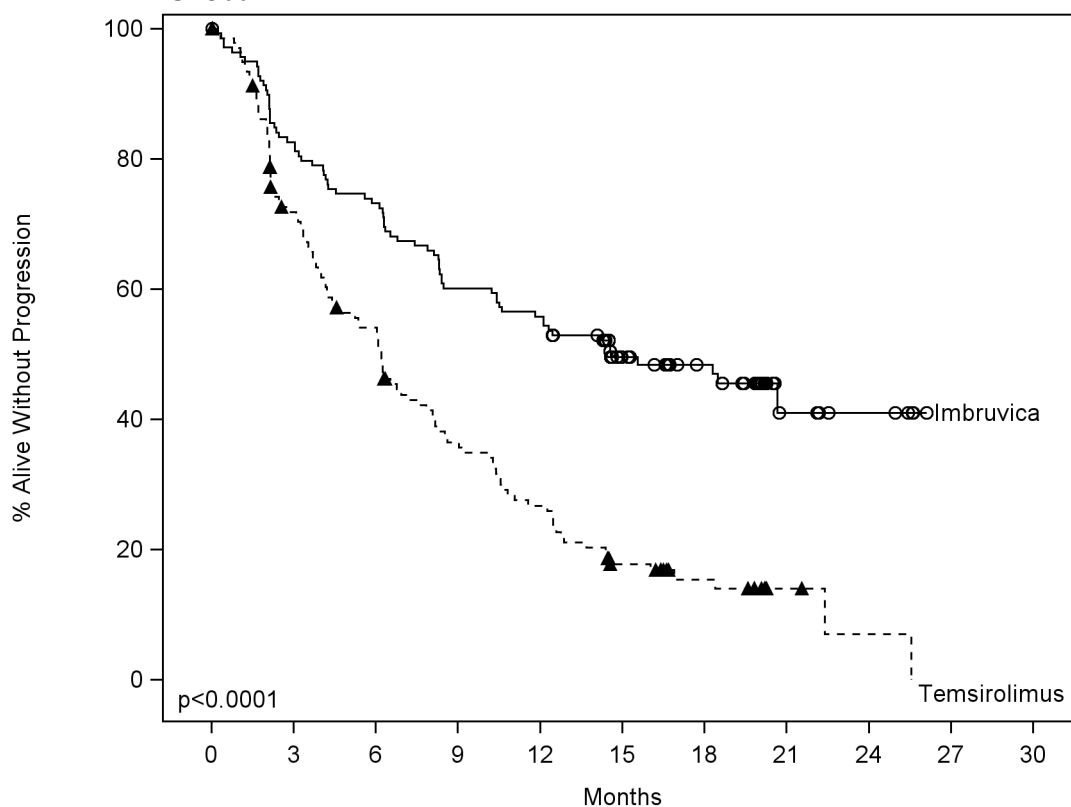
Endpoint	IMBRUVICA N = 139	Temsirolimus N = 141
Progression-Free Survival^a		
Median Progression-Free Survival (95% CI), (months)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
	HR = 0.43 [95% CI: 0.32, 0.58]	
Overall Response Rate (%)	71.9	40.4
p-value	p < 0.0001	

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



Subjects at risk		0	3	6	9	12	15	18	21	24	27	30
Imbruvica	139	114	101	83	77	45	34	8	5	0	0	0
Tamsirolimus	141	93	69	45	33	19	11	3	1	0	0	0

—○— Imbruvica - -▲- - Tamsirolimus

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 inpatient 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

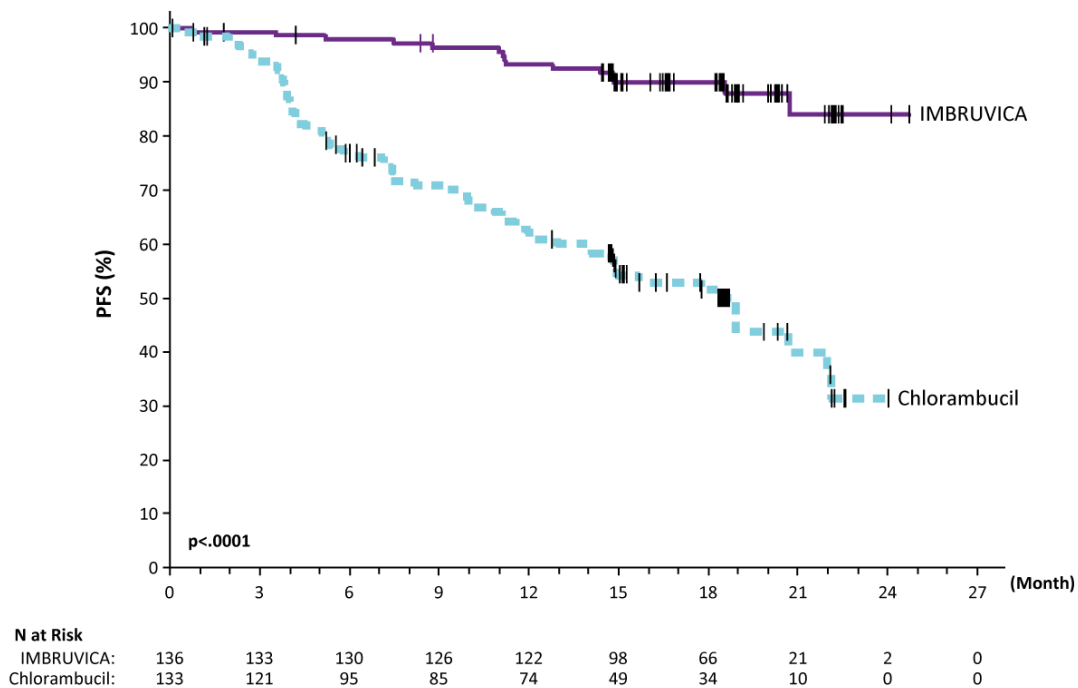
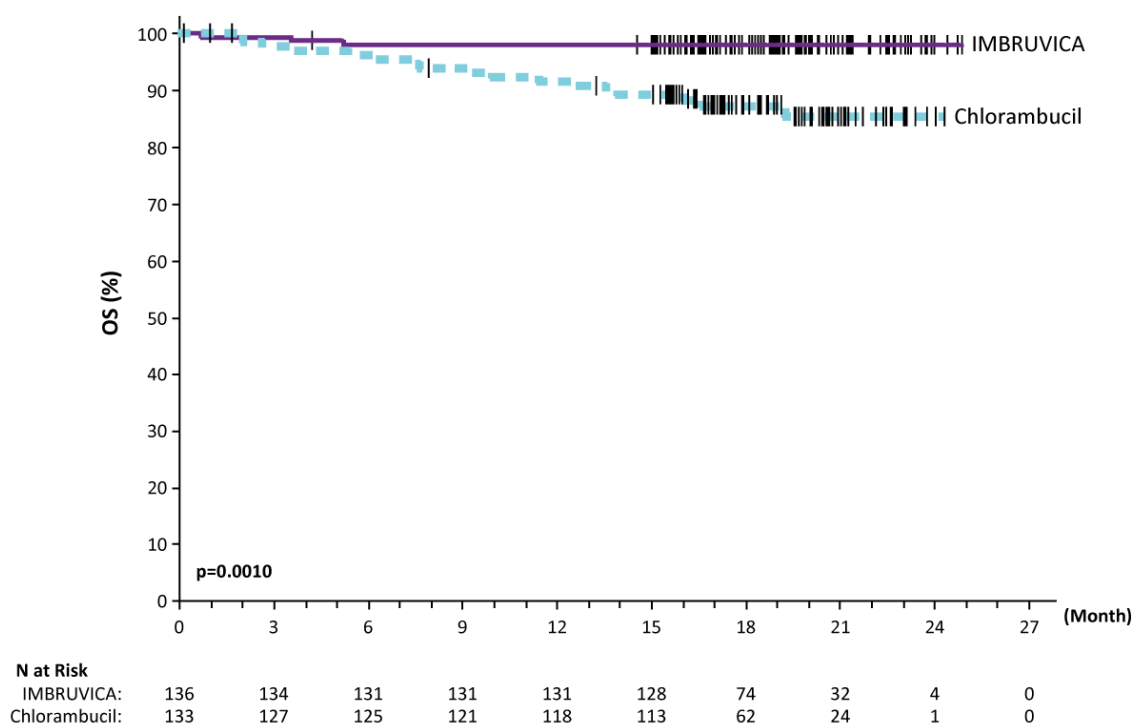


Figure 3: Kaplan-Meier curve of overall survival (ITT Population) in Study PCYC-1115-CA



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).

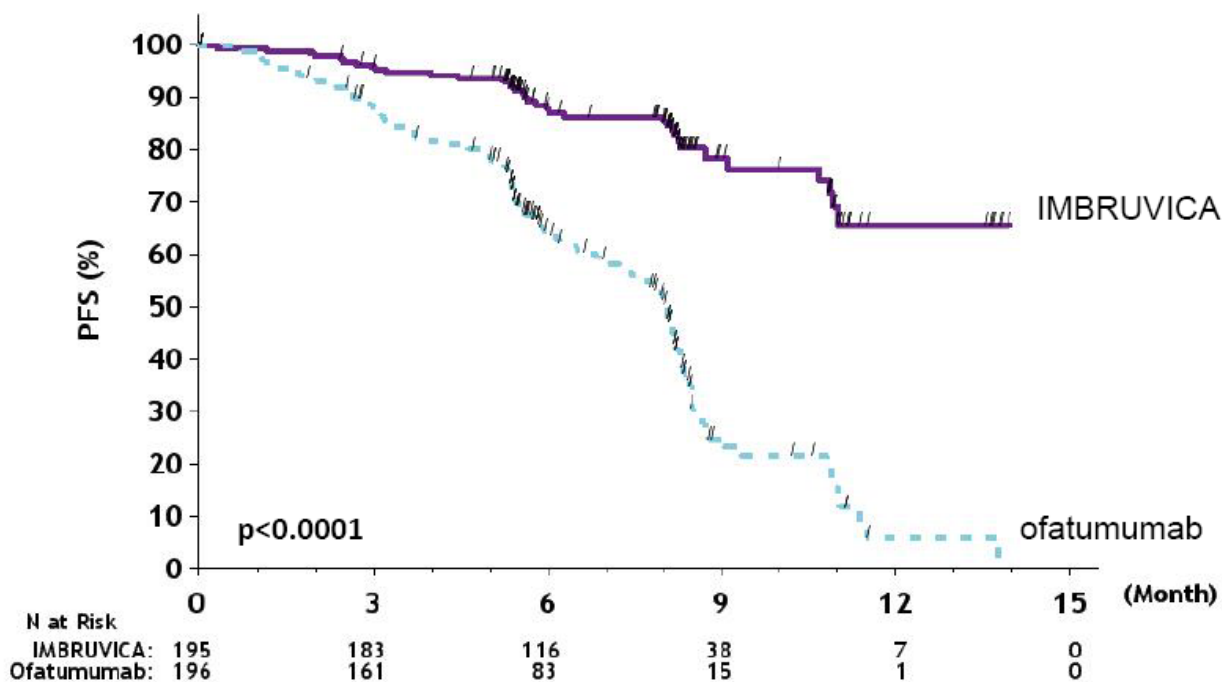
Table 6: Subgroup analysis of progression free survival (Study PCYC-1112-CA)

	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/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 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.

Waldenström's macroglobulinaemia

The safety and efficacy of IMBRUVICA in WM (IgM-excreting lymphoplasmacytic lymphoma) were evaluated in an open-label, multi-center, single-arm trial 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, and 60% of patients were anemic (haemoglobin \leq 11 g/dL or 6.8 mmol/L).

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 Waldenström's macroglobulinaemia. Responses to IMBRUVICA are shown in Table 8.

Table 8: Overall response rate (ORR) and duration of response (DOR) in patients with WM

	Total (N = 63)
ORR (%)	87.3
95% CI (%)	(76.5, 94.4)
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; 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 Independent Review Committee (IRC) demonstrating an ORR of 83%, with a 11% VGPR rate and a 51% PR rate.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IMBRUVICA in all subsets of the paediatric population in MCL, CLL and lymphoplasmacytic lymphoma (LPL) (see section 4.2 for information on paediatric use).

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 \pm standard deviation) 953 \pm 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 [¹⁴C]-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 sternbrae) 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

3 years.

6.4 Special precautions for storage

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.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Submission of yearly updates of study 1112 results for progression and death - to be provided until maturity in the ibrutinib arm, e.g. 70%, and preferably also include PFS2, or, at least, time on next therapy.	4Q 2017

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg hard capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 hard capsules
120 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

imbruvica

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

IMBRUVICA 140 mg capsules
ibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 140 mg of ibrutinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

90 capsules
120 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/945/001 (90 hard capsules)
EU/1/14/945/002 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IMBRUVICA 140 mg hard capsules ibrutinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What IMBRUVICA is and what it is used for
2. What you need to know before you take IMBRUVICA
3. How to take IMBRUVICA
4. Possible side effects
5. How to store IMBRUVICA
6. Contents of the pack and other information

1. What IMBRUVICA is and what it is used for

What IMBRUVICA is

IMBRUVICA is an anticancer medicine that contains the active substance ibrutinib. It belongs to a class of medicines called protein kinase inhibitors.

What IMBRUVICA is used for

It is used to treat the following blood cancers in adults:

- Mantle Cell Lymphoma (MCL), a type of cancer affecting the lymph nodes, when the disease has come back or has not responded to treatment.
- Chronic Lymphocytic Leukaemia (CLL) a type of cancer affecting white blood cells called lymphocytes that also involves the lymph nodes. IMBRUVICA is used in patients who have not previously been treated for CLL or when the disease has come back or has not responded to treatment.
- Waldenström's macroglobulinaemia (WM), a type of cancer affecting white blood cells called lymphocytes. It is used when the disease has come back or has not responded to treatment or in patients for whom chemotherapy given together with an antibody is not a suitable therapy.

How IMBRUVICA works

In MCL, CLL and WM, IMBRUVICA works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, IMBRUVICA helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.

2. What you need to know before you take IMBRUVICA

Do not take IMBRUVICA

- if you are allergic to ibrutinib or any of the other ingredients of this medicine (listed in section 6)

- if you are taking a herbal medicine called St. John’s Wort, used for depression. If you are not sure about this, talk to your doctor, pharmacist or nurse before taking this medicine.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking IMBRUVICA:

- if you have ever had unusual bruising or bleeding or are on any medicines or supplements that increase your risk of bleeding (see section “**Other medicines and IMBRUVICA**”)
- if you have irregular heart beat or have a history of irregular heart beat or severe heart failure, or if you feel any of the following: shortness of breath, weakness, dizziness, light-headedness, fainting or near fainting, chest pain or swollen legs
- if you have liver or kidney problems
- if you have recently had any surgery, especially if this might affect how you absorb food or medicines from your stomach or gut
- if you are planning to have any surgery– your doctor may ask you to stop taking IMBRUVICA for a short time.
- if you have ever had or might now have a hepatitis B infection. This is because IMBRUVICA could cause hepatitis B to become active again. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

When taking IMBRUVICA, tell your doctor immediately if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Tests and check-ups before and during treatment

Tumour lysis syndrome (TLS): Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your doctor or another healthcare provider may do blood tests to check for TLS.

Lymphocytosis: Laboratory tests may show an increase in white blood cells (called “lymphocytes”) in your blood in the first few weeks of treatment. This is expected and may last for a few months. This does not necessarily mean that your blood cancer is getting worse. Your doctor will check your blood counts before or during the treatment and in rare cases they may need to give you another medicine. Talk to your doctor about what your test results mean.

Children and adolescents

IMBRUVICA should not be used in children and adolescents. This is because it has not been studied in these age groups.

Other medicines and IMBRUVICA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, herbal medicines and supplements. This is because IMBRUVICA may affect the way some other medicines work. Also some other medicines can affect the way IMBRUVICA works.

IMBRUVICA may make you bleed more easily. This means you should tell your doctor if you take other medicines that increase your risk of bleeding. This includes:

- acetyl salicylic acid and non-steroidal anti-inflammatories (NSAIDs) such as ibuprofen or naproxen
- blood thinners such as warfarin, heparin or other medicines for blood clots
- supplements that may increase your risk of bleeding such as fish oil, vitamin E or flaxseed.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

Also tell your doctor if you take any of the following medicines – The effects of IMBRUVICA or other medicines may be influenced if you take IMBRUVICA together with any of the following medicines:

- medicines called antibiotics to treat bacterial infections – clarithromycin, telithromycin, ciprofloxacin, erythromycin or rifampicin
- medicines for fungal infections – ketoconazole, itraconazole, fluconazole or voriconazole
- medicines for HIV infection – ritonavir, cobicistat, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, darunavir/ritonavir or fosamprenavir
- medicines to prevent nausea and vomiting associated with chemotherapy - aprepitant
- medicines for depression - nefazodon
- medicines called kinase inhibitors for treatment of other cancers – crizotinib or imatinib
- medicines called calcium channel blockers for high blood pressure or chest pain – diltiazem or verapamil
- medicines called statins to treat high cholesterol - rosuvastatin
- heart medicines/anti-arrhythmics – amiodarone or dronedarone
- medicines to prevent seizures or to treat epilepsy, or medicines to treat a painful condition of the face called trigeminal neuralgia – carbamazepine or phenytoin.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking IMBRUVICA.

If you are taking digoxin, a medicine used for heart problems, or methotrexate, a medicine used to treat other cancers and to reduce the activity of the immune system (e.g., for rheumatoid arthritis or psoriasis), it should be taken at least 6 hours before or after IMBRUVICA.

IMBRUVICA with food

Do not take IMBRUVICA with grapefruit or Seville oranges (bitter oranges) – this includes eating them, drinking the juice or taking a supplement that might contain them. This is because it can increase the amount of IMBRUVICA in your blood.

Pregnancy, breast-feeding and fertility

Do not get pregnant while you are taking this medicine. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.

IMBRUVICA should not be used during pregnancy. There is no information about the safety of IMBRUVICA in pregnant women.

Women of childbearing age must use a highly effective method of birth control during and up to three months after receiving IMBRUVICA, to avoid becoming pregnant while being treated with IMBRUVICA. If using hormonal contraceptives such as birth control pills or devices, a barrier method of contraception (e.g. condoms) must also be used.

- Tell your doctor immediately if you become pregnant.
- Do not breast-feed while you are taking this medicine.

Driving and using machines

You may feel tired or dizzy after taking IMBRUVICA, which may affect your ability to drive or use any tools or machines.

3. How to take IMBRUVICA

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

Mantle Cell Lymphoma (MCL)

The recommended dose of IMBRUVICA is four capsules (560 mg) once a day.

Chronic Lymphocytic Leukaemia (CLL)/Waldenström's macroglobulinaemia (WM)

The recommended dose of IMBRUVICA is three capsules (420 mg) once a day.

Your doctor may adjust your dose.

Taking this medicine

- Take the capsules orally (by mouth) with a glass of water.
- Take the capsules about the same time each day.
- Swallow the capsules whole. Do not open, break or chew them.

If you take more IMBRUVICA than you should

If you take more IMBRUVICA than you should, talk to a doctor or go to a hospital straight away. Take the capsules and this leaflet with you.

If you forget to take IMBRUVICA

- If you miss a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.
- Do not take a double dose to make up for a forgotten dose.
- If you are not sure, talk to your doctor, pharmacist or nurse about when to take your next dose.

If you stop taking IMBRUVICA

Do not stop taking this medicine unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Stop taking IMBRUVICA and tell a doctor straight away if you notice any of the following side effects:

itchy bumpy rash, difficulty breathing, swelling of your face, lips, tongue or throat – you may be having an allergic reaction to the medicine.

Tell a doctor straight away if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)

- fever, chills, body aches, feeling tired, cold or flu symptoms, being short of breath – these could be signs of an infection (viral, bacterial or fungal). These could include infections of the nose, sinus or throat (upper respiratory tract infection), or lung, or skin.
- bruising or increased tendency of bruising.

Common (may affect more than 1 in 100 people)

- severe infections throughout the body (sepsis)
- infections of the urinary tract
- nose bleeds, small red or purple spots caused by bleeding under the skin

- blood in your stools or urine, heavier periods, bleeding that you cannot stop from an injury, confusion, headache with slurred speech or feeling faint – these could be signs of serious internal bleeding in your stomach, gut or brain
- fast heart rate, missed heart beats, weak or uneven pulse (symptoms of atrial fibrillation)
- an increase in the number or proportion of white blood cells shown in blood tests
- low white blood cell counts with fever (febrile neutropenia)
- unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment (tumour lysis syndrome)
- non-melanoma skin cancer, most frequently squamous cell and basal cell skin cancer
- feeling dizzy
- blurred vision
- high blood pressure
- redness of the skin
- high level of “uric acid” in the blood (shown in blood tests), which may cause gout
- inflammation within the lungs that may lead to permanent damage
- breaking of the nails.

Uncommon (may affect more than 1 in 1,000 people)

- severely increased white blood cell count that may cause cells to clump together
- allergic reaction, sometimes severe, that may include a swollen face, lip, mouth, tongue or throat, difficulty swallowing or breathing, itchy rash (hives).

Other very common side effects

- mouth sores
- headache
- constipation
- feeling or being sick (nausea or vomiting)
- diarrhoea, your doctor may need to give you a fluid and salt replacement or another medicine
- skin rash
- painful arms or legs
- back pain or joint pain
- muscle cramps, aches or spasms
- low number of cells that help blood clot (platelets), very low number of white blood cells – shown in blood tests
- swollen hands, ankles or feet.

Not known (frequency cannot be estimated from available data)

- liver failure
- severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store IMBRUVICA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What IMBRUVICA contains

- The active substance is ibrutinib. Each hard capsule contains 140 mg of ibrutinib.
- The other ingredients are:
 - capsule content: croscarmellose sodium, magnesium stearate, microcrystalline cellulose and sodium lauril sulfate
 - capsule shell: gelatin and titanium dioxide (E171)
 - printing ink: shellac, iron oxide black (E172), and propylene glycol.

What IMBRUVICA looks like and contents of the pack

IMBRUVICA are white opaque, hard capsules marked with “ibr 140 mg” in black ink on one side. The capsules are provided in a plastic bottle with a child resistant polypropylene closure. Each bottle contains either 90 or 120 capsules. Each pack contains one bottle.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for ibrutinib, the scientific conclusions of CHMP are as follows:

Hepatitis B reactivation

In the context of this PSUR, the MAH has performed a cumulative review of all cases of hepatitis B reactivation. On a total population of 1741 patients enrolled in clinical trials, HBV reactivation was reported in only 2 subjects. However, it is noted that candidate subjects for clinical trials had been screened for signs of prior or acute hepatitis infection (hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody) and that patients who resulted positive for hepatitis B core antibody or hepatitis B surface antigen were required to have a negative polymerase chain reaction (PCR) to be eligible for enrolment in clinical trial. With regards to individual case safety reports, 8 cases of hepatitis B reactivation (including one fatal case) were reported, in which the treating physician/investigator considered the role of ibrutinib as probable/possible (7 cases) or related. Given the evidence reported in post-marketing settings, the HBV pre-screening of patients to be enrolled in clinical trials operated by the MAH and the impossibility to exclude a causative role played by ibrutinib in cases of hepatitis b reactivation, this safety concern should be listed in section 4.8 of the SmPC with frequency 'uncommon'. In addition, the PRAC considered that healthcare professionals should be informed about the risk of viral reactivation and that a warning should be introduced in the product information.

Ventricular tachyarrhythmia

52 cases of ventricular tachyarrhythmia were reported in post-marketing settings of which the role of ibrutinib could not be ruled out in 2 cases. Also a recent study by Lampson and colleagues (2016) reports 11 cases of Ventricular tachycardia/ ventricular fibrillation and 6 cases of sudden cardiac death in patients exposed to ibrutinib. In 12 of the total 17 cases, the events above occurred without any evidence of prior cardiac history. Finally, atrial fibrillation is included as an important identified risk- and 'cardiac arrhythmia (excluding cardiac fibrillation)' as an important potential risk in the RMP. Atrial fibrillation is also reported in section 4.4 of the SmPC and listed as 'common' in section 4.8 of the SmPC. Therefore, although the biological mechanism is still not clear, it cannot be excluded that ibrutinib might have general pro-arrhythmogenic properties. Based on this outcome, update of section 4.4 and 4.8 of the Summary of product characteristic to include the risk of ventricular tachyarrhythmia is recommended.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing ibrutinib were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ibrutinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ibrutinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.