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 is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

**IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.**

IMBRUVICA 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 (WM)*
The recommended dose for the treatment of CLL and 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:

<table>
<thead>
<tr>
<th>Toxicity occurrence</th>
<th>MCL dose modification after recovery</th>
<th>CLL/WM dose modification after recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>restart at 560 mg daily</td>
<td>restart at 420 mg daily</td>
</tr>
<tr>
<td>Second</td>
<td>restart at 420 mg daily</td>
<td>restart at 280 mg daily</td>
</tr>
<tr>
<td>Third</td>
<td>restart at 280 mg daily</td>
<td>restart at 140 mg daily</td>
</tr>
<tr>
<td>Fourth</td>
<td>discontinue IMBRUVICA</td>
<td>discontinue IMBRUVICA</td>
</tr>
</tbody>
</table>

**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 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.

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

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

*Effects on the QT interval*

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

*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.

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<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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.

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

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

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

### 4.6 Fertility, pregnancy and lactation

**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 male or female fertility studies have been conducted (see section 5.3).

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 420 patients treated with IMBRUVICA in three phase 2 clinical studies and one randomised phase 3 study 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 drug reactions (≥ 20%) were neutropenia, anaemia, diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea and pyrexia. The most common grade 3/4 adverse drug reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia.

Tabulated list of adverse drug reactions
Treatment-emergent adverse drug reactions for MCL, CLL or WM 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 Treatment-emergent adverse reactions in patients treated with ibrutinib for MCL, CLL or WM (N = 420) and post-marketing adverse reactions

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency (All grades)</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Very common</td>
<td>Pneumonia*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinusitis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin infection*</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Sepsis*</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphocytosis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Leukostasis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperuricaemia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tumour lysis syndrome</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>
### Vascular disorders
- Very common: Haemorrhage*
  - Epistaxis
  - Bruising*
  - Petechiae
- Common: Subdural haematoma

### Gastrointestinal disorders
- Very common: Diarrhoea
- Common: Vomiting
- Uncommon: Stomatitis*
- Not known: Nausea
- Uncommon: Constipation

### Skin and subcutaneous tissue disorders
- Very common: Rash*
- Uncommon: Angioedema
- Not known: Urticaria

### Musculoskeletal and connective tissue disorders
- Very common: Arthralgia
- Uncommon: Musculoskeletal pain*

### General disorders and administration site conditions
- Very common: Pyrexia
- Not known: Oedema peripheral

* Includes multiple adverse drug reaction terms.

**Discontinuation and dose reduction due to adverse reactions**

Of the 420 patients treated with IMBRUVICA for CLL, MCL or WM 4% discontinued treatment primarily due to adverse drug reactions. These included infections and subdural haematoma. Adverse drug reactions leading to dose reduction occurred in approximately 7% of patients.

**Elderly**

Of the 420 patients treated with IMBRUVICA, 59% were above 65 years of age. Grade 3 or higher adverse drug reactions occurred more frequently among elderly patients treated with IMBRUVICA (53% of patients age ≥ 65 versus 42% of younger patients). Grade 3 or higher adverse drug reactions occurring more frequently among elderly patients were pneumonia, atrial fibrillation and urinary tract infection.

**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). 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 few weeks of IMBRUVICA therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in patients with MCL and 18.7 weeks in patients with CLL. 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 WM treated with IMBRUVICA.

**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)

<table>
<thead>
<tr>
<th></th>
<th>Total N = 111</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>67.6</td>
</tr>
<tr>
<td>95% CI (%)</td>
<td>(58.0; 76.1)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>20.7</td>
</tr>
<tr>
<td>PR (%)</td>
<td>46.8</td>
</tr>
<tr>
<td>Median DOR (CR+PR) (months)</td>
<td>17.5 (15.8, NR)</td>
</tr>
<tr>
<td>Median time to initial response, months (range)</td>
<td>1.9 (1.4-13.7)</td>
</tr>
<tr>
<td>Median time to CR, months (range)</td>
<td>5.5 (1.7-11.5)</td>
</tr>
</tbody>
</table>

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.
**Chronic lymphocytic leukaemia**

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 (\( \geq 5 \) cm), 35.3% had deletion 17p and 31.4% had deletion 11q. ORR was assessed according to the 2008 International Workshop on CLL (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 \( \geq 5 \) 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 3.

**Table 3: Efficacy results in patients with chronic lymphocytic leukaemia (Study PCYC-1112-CA)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>IMBRUVICA N = 195</th>
<th>Ofatumumab N = 196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression free survival</td>
<td>Not reached</td>
<td>8.1 months</td>
</tr>
<tr>
<td>Overall survival(^a)</td>
<td>HR = 0.215 [95% CI: 0.146; 0.317]</td>
<td>HR = 0.434 [95% CI: 0.238; 0.789](^b)</td>
</tr>
<tr>
<td>Overall response rate(^d), (^e) (%)</td>
<td>42.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Overall response rate including PR with lymphocytosis(^d), (^e) (%)</td>
<td>62.6</td>
<td>4.1</td>
</tr>
</tbody>
</table>

\(^a\) 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 4).
Table 4: Subgroup analysis of progression free survival (Study PCYC-1112-CA)

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

Hazard ratio based on non-stratified analysis

The Kaplan-Meier curve for PFS is shown in Figure 1.

Figure 1: Kaplan-Meier curve of progression-free survival (ITT Population) in Study PCYC-1112-CA

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 ≤ 11 g/dL).

IMBRUVICA was administered orally at 420 mg once daily until disease progression or unacceptable toxicity. The primary endpoint in this study was ORR per investigator assessment. The ORR and DOR
were assessed using criteria adopted from the Third International Workshop of Waldenström’s macroglobulinaemia. Responses to IMBRUVICA are shown in Table 5.

| Table 5: Overall response rate (ORR) and duration of response (DOR) in patients with WM |
|-------------------------------------------------|------------------|
| ORR (%)                                         | Total (N = 63)   |
| 95% CI (%)                                      | 87.3             |
| VGPR (%)                                        | (76.5, 94.4)     |
| 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<sub>max</sub> 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<sub>last</sub>) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast.

Distribution

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state (V<sub>d,ss</sub>/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 \( (AUC_{\text{last}}) \) was observed in subjects with mild \( (n = 6, \text{Child-Pugh class A}) \), moderate \( (n = 10, \text{Child-Pugh class B}) \) and severe \( (n = 8, \text{Child-Pugh class C}) \) 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 \( (AUC_{\text{unbound, last}}) \) 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 inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that the medicinal product has any clinically relevant drug-drug interactions with medicinal products that may be metabolised by the CYP450 enzymes.

**Co-administration with transport substrates/inhibitors**
*In vitro* studies indicated that ibrutinib is not a substrate of P-gp, OATP1B1 and OATP1B3. Ibrutinib is an *in vitro* inhibitor of P-gp (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).

Fertility
Fertility studies with ibrutinib have not been conducted.

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

2 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

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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Obligation to conduct post-authorisation measures

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission of the final study report of study MCL3001</td>
<td>1Q 2016</td>
</tr>
<tr>
<td>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.</td>
<td>2Q 2015</td>
</tr>
</tbody>
</table>
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
### 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  
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
B. PACKAGE LEAFLET
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. It is used when the disease has come back or has not responded to treatment or in patients with high risk CLL (patients whose cancer cells have certain DNA changes called “17p deletion” or “TP53 mutation”) for whom chemotherapy given together with an antibody is not a suitable therapy.
- Waldenström’s macroglobulinaemia, 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 and CLL, 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.
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 a history of irregular heart beat (atrial fibrillation) or severe heart failure, which makes you short of breath and may lead to 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 any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

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 – they can increase or decrease the amount of IMBRUVICA in your blood:

- 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
- 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, 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, 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.

### 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 lung, the nose, sinus or throat (upper respiratory tract infection), or urinary tract or sinus, or skin.
● nose bleeds, bruising or increased tendency of bruising or small red or purple spots caused by bleeding under the skin.

Common (may affect more than 1 in 100 people)
● severe infections throughout the body (sepsis)
● 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)
● blurred vision
● dry mouth
● not having enough water in the body (dehydration)
● high level of “uric acid” in the blood (shown in blood tests), which may cause gout.
Uncommon (may affect more than 1 in 1,000 people)
● severely increased white blood cell count that may cause cells to clump together
● 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)
● 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 or feeling dizzy
● 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 or aches
● low number of cells that help blood clot (platelets), very low number of white blood cells, low number of red blood cells (anaemia) – shown in blood tests
● swollen hands, ankles or feet.

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 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.
Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Pharmaceutica NV
Turnhoutseweg 30
2340 Beerse
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Antwerpseweg 15-17
B-2340 Beerse
Tel/Tél: +32 14 64 94 11

Lietuva
UAB „Johnson & Johnson“
Geležinio Vilko g. 18A
LT-08104 Vilnius
Tel: +370 5 278 68 88

Bulgaria
„Джонсън & Джонсън България” ЕООД
ж.к. Младост 4
Бизнес Парк София, града 4
София 1766
Тел.: +359 2 489 94 00

Luxembourg/Luxemburg
Janssen-Cilag NV
Antwerpseweg 15-17
B-2340 Beerse
Belgique/Belgien
Tél/Tel: +32 14 649 411

Česká republika
Janssen-Cilag s.r.o.
Karla Engliše 3201/06
CZ-150 00 Praha 5 - Smíchov
Tel. +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Nagyenyed u. 8-14
H-Budapest, 1123
Tel.: +36 1 884 2858

Danmark
Janssen-Cilag A/S
Bregnerødvej 133
DK-3460 Birkerød
Tlf: +45 45 94 82 82

Malta
Am Mangion Ltd.
Mangion Building, Triq Ġdida fi Triq Valletta
MT-Hal-Luqa LQA 6000
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Johnson & Johnson Platz 1
D-41470 Neuss
Tel: +49 2137 955 955

Nederland
Janssen-Cilag B.V.
Dr. Paul Janssenweg 150
NL-5026 RH Tilburg
Tel: +31 13 583 73 73

Eesti
Janssen-Cilag Polska Sp. z o.o. Eesti filial
Lõõtsa 2
EE-11415 Tallinn
Tel: +372 617 7410

Norge
Janssen-Cilag AS
Postboks 144
NO-1325 Lysaker
Tlf: +47 24 12 65 00
Ελλάδα
Janssen-Cilag Φαρμακευτική Α.Ε.Β.Ε.
Δευτερόλευκης Ειρήνης 56
GR-151 21 Πεύκη, Αθήνα
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Paseo de las Doce Estrellas, 5-7
E-28042 Madrid
Tel: +34 91 722 81 00

France
Janssen-Cilag
1, rue Camille Desmoulins, TSA 91003
F-92787 Issy Les Moulineaux, Cedex 9
Tél: 0 800 25 50 75 / +33 1 55 00 40 03

Hrvatska
Johnson & Johnson S.E. d.o.o.
Oreškovićeva 6H
HR-10010 Zagreb
Tel: + 385 1 66 10 700

Ireland
Janssen-Cilag Ltd.
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire HP12 4EG
United Kingdom
Tel: +44 1494 567 567

Ísland
Janssen-Cilag AB
c/o Vistor hf.
Hörgatún 2
IS-210 Gardabaer
Sími: +354 535 7000

Italia
Janssen-Cilag SpA
Via M.Buonarroti, 23
I-20093 Cologno Monzese MI
Tel: +39 02 2510 1

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Δευτερόλευκος Γιάννου Κρανιδιώτη 226
Λατσιά
CY-2234 Λευκωσία
Τηλ: ++357 22 207 700

Österreich
Janssen-Cilag Pharma GmbH
Vorgartenstraße 206B
AT-1020 Wien
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
ul. Ilżecka 24
PL-02-135 Warszawa
Tel.+48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Estrada Consiglieri Pedroso, 69 A
Queluz de Baixo
PT-2734-503 Barcarena
Tel: +351 21 43 68 835

România
Johnson & Johnson România SRL
Strada Tipografilor Nr. 11-15
Clădirea S-Park, Corp A2, Etaj 5
013714 București, ROMANIA
Tel: +40 21 207 18 00

Slovenija
Johnson & Johnson d.o.o.
Šmartinska cesta 53
SI-1000 Ljubljana
Tel: +386 1 401 18 30

Slovenská republika
Johnson & Johnson, s.r.o.
CBC III, Karadžičova 12
SK-821 08 Bratislava
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Vaisalantie/Vaisalavägen 2
FI-02130 Espoo/Esbo
Puh/Tel: +358 207 531 300

Sverige
Janssen-Cilag AB
Box 7073
SE-192 07 Sollentuna
Tel: +46 8 626 50 00
This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: