PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

IMBRUVICA® 140 mg film-coated tablets

IMBRUVICA® 420 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMBRUVICA 140 mg film-coated tablets

Each film-coated tablet contains 140 mg of ibrutinib.

Excipients with known effect

Each 140 mg film-coated tablet contains:

- 28 mg of lactose monohydrate and
- a total of 1,14 mg sodium, which is comprised of 0,98 mg from sodium (7 g/100 g) and 0,16 mg from sodium lauryl sulphate (1 g contains 0,08 g sodium).

IMBRUVICA 420 mg film-coated tablets

Each film-coated tablet contains 420 mg of ibrutinib.

Excipients with known effect

Each 420 mg film-coated tablet contains:

- 84 mg of lactose monohydrate and
- a total of 3,42 mg sodium which is comprised of 2,94 mg from sodium (7 g/100 g) and 0,48 mg from sodium lauryl sulphate (1 g contains 0,08 g sodium).

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

IMBRUVICA 140 mg film-coated tablets

Yellow-green to green round tablets (9 mm), debossed with “ibr” on one side and “140” on the other side.

IMBRUVICA 420 mg film-coated tablets

Yellow-green to green oblong tablets (17,5 mm in length and 7,4 mm in width), debossed with “ibr” on one side and “420” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMBRUVICA is indicated for:

Mantle Cell Lymphoma (MCL)

- as a single agent in adult patients for relapsed or refractory mantle cell lymphoma, who have received at least one prior therapy.
- in combination with bendamustine and rituximab (BR) for patients with previously untreated MCL.

Chronic Lymphocytic Leukaemia (CLL)

- as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- as a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy.

Waldenström's Macroglobulinaemia (WM)

- as a single agent 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.
- in combination with rituximab for the treatment of adult patients with WM.

4.2 Posology and method of administration

Posology

Mantle cell lymphoma

The recommended dose of IMBRUVICA for the treatment of MCL is 560 mg once daily until disease progression or no longer tolerated by the patient.

For additional information concerning rituximab, bendamustine (BR), see the corresponding rituximab or bendamustine prescribing information.

Chronic lymphocytic leukaemia (CLL)

The recommended dose of IMBRUVICA for treatment naïve or previously treated CLL, either as a single agent or in combination (see section 4.1), is 420 mg orally once daily until disease progression or no longer tolerated by the patient.

In combination with venetoclax, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax.

For additional information concerning BR, venetoclax or obinutuzumab see the corresponding rituximab, bendamustine, venetoclax or obinutuzumab prescribing information.

When administering IMBRUVICA in combination with anti-CD20 therapy, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Waldenström's Macroglobulinaemia (WM)

The recommended dose of IMBRUVICA for treatment naïve or previously treated WM, either as a single agent or in combination (see section 4.1), is 420 mg orally once daily until disease progression or no longer tolerated by the patient.

For additional information concerning BR, or obinutuzumab see the corresponding rituximab, bendamustine, or obinutuzumab prescribing information.

When administering IMBRUVICA in combination with anti-CD20 therapy, it is recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

Dose modification guidelines

Dose modifications are required for the concomitant use of moderate and strong CYP3A inhibitors as these can increase the exposure of ibrutinib (see section 4.5).

IMBRUVICA therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade 3 cardiac dysrrhythmias, Grade ≥ 3 non-haematological toxicities, 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), resume IMBRUVICA therapy at the recommended dose as per the tables below.

Recommended dose modifications for non-cardiac events are described below:

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/WM dose modification after recovery
Grade 3 or 4 non-haematological toxicities Grade 3 or 4 neutropenia with infection or fever Grade 4 haematological toxicities	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	
* When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.			

Recommended dose modifications for events of cardiac failure or cardiac dysrhythmias are described below:

Events	Toxicity occurrence	MCL dose modification after recovery	CLL/WM dose modification after recovery
Grade 2 cardiac failure	First	restart at 420 mg daily	restart at 280 mg daily
	Second	restart at 280 mg daily	restart at 140 mg daily
	Third	discontinue IMBRUVICA	
Grade 3 cardiac dysrhythmias	First	restart at 420 mg daily†	restart at 280 mg daily†
	Second	discontinue IMBRUVICA	

Grade 3 or 4 cardiac failure Grade 4 cardiac dysrhythmias	First	discontinue IMBRUVICA
† Evaluate the benefit-risk before resuming treatment.		

Missed dose

If a dose of IMBRUVICA 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 doses to make up the missed dose.

Special populations

Paediatrics (18 years of age and younger)

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

Renal impairment

IMBRUVICA has minimal renal clearance. No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in 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. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Hepatic impairment

IMBRUVICA 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. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. 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). Cases of hepatic failure including fatal outcome have occurred in patients treated with IMBRUVICA (see section 4.8).

Method of administration

IMBRUVICA should be administered orally once daily with a glass of water at approximately the same time each day. The tablets should be swallowed whole with water and should not be broken or chewed. IMBRUVICA must not be taken with grapefruit juice or Seville oranges. IMBRUVICA should continue until disease progression or no longer tolerated by the patient.

4.3 Contraindications

IMBRUVICA is contraindicated in:

- Patients who have known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to ibrutinib or to any of the excipients listed in section 6.1.
- Pregnancy and Lactation (see section 4.6).
- Concomitant use with strong CYP3A inhibitors should be avoided (see section 4.5).
- Concomitant use with preparations containing St. John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

Bleeding-related events

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

In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA. Monitor for signs and symptoms of bleeding.

Supplements such as fish oil and vitamin E preparations should be avoided.

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

Patients with congenital bleeding diathesis have not been studied.

Spinal anaesthesia and epidural anaesthesia are not recommended for patients receiving IMBRUVICA.

Leukostasis

Leukostasis syndrome is characterised by a clinically significant elevated white cell count, with abnormal intravascular leukocyte aggregation and symptoms of decreased tissue perfusion caused by microinfarction. Cases of leukostasis have been reported in patients treated with IMBRUVICA. A high number of circulating lymphocytes (> 400 000/µL) may confer increased risk. Consider temporarily withholding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Splenic rupture

Cases of splenic rupture have been reported following discontinuation of IMBRUVICA treatment. Disease status and spleen size should be carefully monitored (e.g., clinical examination, ultrasound) when IMBRUVICA treatment is interrupted or ceased. Patients who develop left upper abdominal or shoulder tip pain should be evaluated, and a diagnosis of splenic rupture should be considered.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA.

Data from one study in elderly patients (≥ 65 years of age) with previously untreated MCL suggest an increased risk of serious or fatal infections, including pneumonia, when IMBRUVICA is used in combination with bendamustine and rituximab, including during rituximab maintenance and ibrutinib monotherapy phase. Patients with diabetes mellitus, COPD/asthma, and/or lymphopenia may be at greater risk for these events, and benefit/risk should be carefully evaluated in these patients. Patients should be closely monitored for infections, including respiratory signs and symptoms throughout treatment, and appropriate anti-infective therapy should be initiated promptly.

Hepatic events

Cases of hepatotoxicity, hepatitis B reactivation, and cases of hepatitis E, which may be chronic, have occurred in patients treated with IMBRUVICA. Hepatic failure including fatal events have occurred in patients treated with IMBRUVICA. Liver function and viral hepatitis status should be assessed before initiating treatment with IMBRUVICA. Patients should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting, jaundice and abnormal liver function tests) and appropriate therapy should be instituted as indicated. As clinically indicated, viral load and serological testing for infectious hepatitis should be performed per medical guidelines. For patients diagnosed with hepatic events, consultation with a physician with expertise in the management of liver disease is recommended.

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 dysrhythmias and cardiac failure

Fatal and serious cardiac dysrhythmias or cardiac failure have occurred in patients treated with IMBRUVICA. Patients with significant cardiac co-morbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachydysrhythmia and cardiac failure have been reported particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac dysrhythmia.

Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating IMBRUVICA. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. Consider the risks and benefits of IMBRUVICA treatment and follow the dose modification guidelines.

In patients who develop signs and/or symptoms of ventricular tachydysrhythmia, 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.

Patients should be monitored for signs and symptoms of cardiac failure during IMBRUVICA treatment. In some of these cases cardiac failure resolved or improved after IMBRUVICA withdrawal or dose reduction.

Class effect of Tyrosine Kinase Inhibitors (TKIs) such as contained in IMBRUVICA

Cases of cerebrovascular accident, transient ischaemic attack, and ischaemic stroke including fatalities have been reported with the use of IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension, although causality with ibrutinib has not been established (see section 4.8, Post-marketing adverse reactions).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs. Patients on treatment with IMBRUVICA should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with IMBRUVICA should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended (see section 4.4, Cardiac dysrhythmias and Hypertension).

Non-melanoma skin cancer

Non-melanoma skin cancers have occurred in patients treated with IMBRUVICA. Monitor patients for the appearance of non-melanoma skin cancer.

Second primary malignancies

Other malignancies have occurred in patients treated with IMBRUVICA.

Tumour lysis syndrome (TLS)

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.

Hypertension

Hypertension has occurred in patients treated with IMBRUVICA. Regularly monitor blood pressure in patients treated with IMBRUVICA and initiate or adjust antihypertensive medication throughout treatment with IMBRUVICA as appropriate.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH (including fatal cases) have been reported in patients treated with IMBRUVICA. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of extreme systemic inflammation. HLH is characterised by fever, hepatosplenomegaly, hypertriglyceridaemia, high serum ferritin and cytopenias. Patients should be informed about symptoms of HLH. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered.

Excipients of known effect

- This medicine contains lactose therefore patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- This medicine contains less than 1 mmol (23 mg) sodium per dose, meaning that it is essentially 'sodium free'. However, patients on a sodium restricted diet should be aware of their daily sodium intake.

4.5 Interaction with other medicines and other forms of interaction

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

Medicines that may increase IMBRUVICA plasma concentrations

Concomitant use of IMBRUVICA and medicines that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A inhibitors should be avoided.

Strong CYP3A inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (C_{max} and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated interaction study in patients with B-cell malignancies, co-administration of voriconazole increased C_{max} and AUC by 6,7-fold and 5,7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n = 47) or strong CYP3A inhibitors (n = 19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with IMBRUVICA as per dose recommendations in the table below. All other strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. **If a strong CYP3A inhibitor must be used, see recommended dose modifications in the table below.**

Moderate and mild CYP3A inhibitors

In patients with B-cell malignancies, co-administration of CYP3A inhibitor erythromycin increased C_{max} and AUC by 3,4-fold and 3,0-fold, respectively. **If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) must be used, reduce IMBRUVICA dose as per recommended dose modifications in the table below.**

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during IMBRUVICA treatment as these contain moderate inhibitors of CYP3A (see sections 4.2 and 5.2).

Recommended dose modifications are described below:

Patient Population	**Co-administered medicine**	**Recommended IMBRUVICA Dose for the Duration of the Inhibitor Use[a]**
B-Cell Malignancies	• Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	• Moderate CYP3A inhibitors	280 mg once daily.
	• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg twice daily.	140 mg once daily.
	• Other strong CYP3A inhibitors • Posaconazole at higher doses[b].	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential.

		If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce IMBRUVICA dose to 140 mg once daily for the duration of the inhibitor use.

[a] Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see section 4.2).

[b] Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of IMBRUVICA (see section 4.2).

Medicines that may decrease IMBRUVICA plasma concentrations

Administration of IMBRUVICA with strong inducers of CYP3A decreases ibrutinib plasma concentrations by approximately 90 %.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampicin, phenytoin and St. John's Wort). Consider alternative medicines with less CYP3A induction.

Medicines that may have their plasma concentrations altered by IMBRUVICA

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward

CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are weak inducers of CYP450 isoenzymes *in vitro*.

However, in a medicine interaction study in patients with B-cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinyl oestradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

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. IMBRUVICA is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). IMBRUVICA is not expected to have systemic interactions with P-gp substrates. However, it cannot be excluded that IMBRUVICA could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimise the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after IMBRUVICA. IMBRUVICA may also inhibit BCRP systemically and increase the exposure of medicines that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. If this medicine is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to a foetus. The time period following treatment with IMBRUVICA where it is safe to become pregnant is unknown.

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

Pregnancy

IMBRUVICA should not be used during pregnancy (see section 4.3).
Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women.

Breastfeeding

Because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, breastfeeding should be discontinued during IMBRUVICA treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trial data

Summary of the safety profile

Adverse reactions from integrated studies in adult patients with B-cell malignancies

The data described below reflect exposure to IMBRUVICA in four phase 2 (PCYC-1102-CA, PCYC-1104-CA, PCYC-1118E, PCYC-1142-CA) and nine phase 3 studies (PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, MCL3001, PCYC-1127-CA, E1912, CLL3011, and MCL3002), that included 2240 patients with B-cell malignancies. Patients received IMBRUVICA until disease progression or unacceptable toxicity.

The most commonly occurring adverse reactions (≥ 20 %) were diarrhoea, neutropenia, rash musculoskeletal pain, haemorrhage (e.g., bruising), nausea, thrombocytopenia, arthralgia upper respiratory tract infection and pyrexia.

The most common Grade 3/4 adverse reactions (≥ 5 %) were neutropenia, lymphocytosis, thrombocytopenia pneumonia, hypertension and rash.

Tabulated summary of adverse reactions

Adverse reactions for MCL, CLL or WM are listed below by system organ class and frequency grouping. Frequency categories are defined as follows: *very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon*

(≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000) and very rare (< 1/10 000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported in clinical studies in patients treated with B-cell malignancies treated with IMBRUVICA (N = 2240)

System organ class	Frequency (All grades)	Adverse reactions
Infections and infestations	Very common	Pneumonia*†
		Upper respiratory tract infection
		Skin infection*
	Common	Sepsis*†
		Urinary tract infection
		Sinusitis*
	Uncommon	Hepatitis B reactivation†
Neoplasms benign and malignant (including cysts and polyps)	Common	Non-melanoma skin cancer*
		Basal cell carcinoma
		Squamous cell carcinoma
Blood and lymphatic system disorders	Very common	Neutropenia*
		Thrombocytopenia*
		Lymphocytosis*
	Common	Febrile neutropenia
		Leukocytosis
	Rare	Leukostasis syndrome

Metabolism and nutrition disorders	Common	Hyperuricaemia
	Uncommon	Tumour lysis syndrome
Nervous system disorders	Very common	Headache Dizziness
Eye disorders	Common	Blurred vision
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage*† Bruising* Hypertension*
	Common	Epistaxis Petechiae
	Uncommon	Subdural haematoma†
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation Dyspepsia
Skin and subcutaneous tissue disorders	Very common	Rash*
	Common	Urticaria Erythema
	Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Muscle spasms Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia Peripheral oedema

Investigations	Very common	Increased blood creatine

* Includes multiple adverse reaction terms.

† Includes events with fatal outcome.

Discontinuation and dose reduction due to adverse reactions

Of the 2240 patients treated with IMBRUVICA for CLL, MCL or WM, 8 % discontinued treatment due to adverse reactions. These included pneumonia, rash atrial fibrillation, neutropenia, thrombocytopenia, haemorrhage, and diarrhoea. Adverse reactions leading to dose reduction occurred in approximately 10 % of patients.

Leukostasis

Isolated cases of leukostasis have been observed (see section 4.4).

Elderly

Of the 2240 patients treated with IMBRUVICA, 55 % were 65 years of age or older. Grade 3 or higher pneumonia occurred more frequently (≥ 5 %) among elderly patients treated with IMBRUVICA (14 % of patients age ≥ 65 versus 4 % of patients < 65 years of age) and thrombocytopenia (12 % of patients ≥ 65 years of age versus 5 % of patients < 65 years of age).

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during post-marketing experience (see Table 2).

Table 2: Adverse reactions identified during post marketing experience with IMBRUVICA

System Organ Class	Adverse Reaction
Eye Disorders	Eye haemorrhage
Cardiac disorders	Ventricular tachydysrhythmias*†
	Cardiac failure
Immune system disorders	Interstitial lung disease*
Metabolism and nutrition disorders	Tumour lysis syndrome
Hepatobiliary disorders	Hepatic failure*,
Skin and subcutaneous tissue disorders	Erythema
	Onychoclasis
	Urticaria
	Angioedema
	Panniculitis*
	Neutrophilic dermatoses*
	Stevens-Johnson syndrome
Nervous system disorders	Peripheral neuropathy*
	Cerebrovascular accident†
	Transient ischaemic attack
	Ischaemic stroke†

** Includes multiple adverse reaction terms.*

† Includes events with fatal outcome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose

There are limited data on the effects of IMBRUVICA overdose. In one study, a healthy subject who received a dose of 1 680 mg experienced reversible Grade 4 hepatic enzyme increases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. Patients who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 26 Cytostatic agents

Mechanism of action

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. Preclinical studies have shown that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro.*

BTK inhibition by ibrutinib increases CLL cell dependence on BCL-2, a cell survival pathway, while venetoclax inhibits BCL-2 leading to apoptosis. In preclinical tumour models, the combination of ibrutinib and venetoclax resulted in increased cellular apoptosis and anti-tumour activity compared to either agent alone.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥ 50 % increase from baseline and an absolute count > 5 000/µL), often associated with reduction of lymphadenopathy, has been observed in most patients (66 %) with chronic lymphocytic leukaemia (CLL). This effect has also been observed in some patients (35 %) with mantle cell lymphoma (MCL) treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8,0 weeks in patients with MCL and 14 weeks in patients with CLL (range, 0,1 to 104 weeks).

When IMBRUVICA was administered in combination with BR or with obinutuzumab in subjects with CLL, lymphocytosis was infrequent (7 % with IMBRUVICA + BR versus 6 % with placebo + BR and 7 % with IMBRUVICA + obinutuzumab versus 1 % with chlorambucil +

obinutuzumab). When IMBRUVICA was administered in combination with BR in subjects with previously untreated MCL, lymphocytosis was reported in 5 % of subjects treated with IMBRUVICA + BR versus 4 % in subjects treated with placebo + BR.

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

5.2 Pharmacokinetic properties

Absorption

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours.

The absolute bioavailability in fasted condition after oral intake of ibrutinib in volunteers (n = 8) was 2,9 % (90 % CI = 2,1 – 3,9) and doubled when combined with a meal.

The 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. The steady state AUC observed in patients at 420 mg is (mean ± standard deviation) 732 ± 521 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.

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 volume of distribution at steady state ($V_{d,ss}$) was 683 L and the apparent volume of distribution at steady-state ($V_{d,ss}/F$) is approximately 10 000 L.

Metabolism

Ibrutinib is metabolised primarily by cytochrome P450, CYP3A4/5, to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Systemic steady-state exposure to the dihydrodiol metabolite is comparable to that of the parent medicine.

In vitro studies indicated that CYP2D6 involvement in ibrutinib oxidative metabolism is < 2 %. Moreover, as part of a human mass balance study, subjects genotyped as poor metabolisers for CYP2D6, showed a similar pharmacokinetic profile as extensive metabolisers. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Elimination

Intravenous clearance was 62 and 76 L/h in fasted and fed condition, respectively. In line with the high first-pass effect, the apparent oral clearance is approximately 2 000 and 1 000 L/h in fasted and fed condition, respectively.

The half-life of ibrutinib is 4 to 6 hours. After a single oral administration of radio labeled [^{14}C]-ibrutinib in healthy subjects, approximately 90 % of radioactivity was excreted within 168 hours, with the majority (80 %) excreted in the faeces and less than 10 % accounted for in urine. Unchanged ibrutinib accounted for approximately 1 % of the radiolabeled

excretion product in faeces and none in urine, with the remainder of the dose being metabolites.

Special populations

Elderly (65 years of age and older)

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

Paediatrics (18 years of age and younger)

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

Renal impairment

Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10 % of the dose. No specific clinical studies have been conducted to date in subjects with impaired renal function. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There are no data in patients with severe renal impairment or patients on dialysis.

Hepatic impairment

Ibrutinib is metabolised in the liver. A hepatic impairment study was performed in non-cancer subjects administered a single dose of 140 mg of ibrutinib under fasting conditions. Ibrutinib AUC_{last} increased 2,7-; 8,2- and 9,8-fold 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulfate (E487)

Film-coat

IMBRUVICA 140 mg film-coated tablets and IMBRUVICA 420 mg film-coated tablets

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Black iron oxide (E172)

Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

IMBRUVICA film-coated tablets are packaged in clear colourless polyvinyl chloride (PVC) laminated with silver coloured polychlorotrifluoroethylene (PCTFE)/aluminum push-through blisters.

28 pack size - for all film-coated tablets strengths: Two blisters with 7 film-coated tablets each in one wallet. Two wallets with 14 tablets in one cardboard carton box.

30 pack size - for all film-coated tablets strengths: Two blisters with 5 film-coated tablets each in one wallet. Three wallets with 10 tablets in one carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION



JANSSEN PHARMACEUTICA (Pty) Ltd.

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8. REGISTRATION NUMBERS

IMBRUVICA® 140 mg film-coated tablets: 55/26/0297

IMBRUVICA® 420 mg film-coated tablets: 55/26/0299

9 DATE OF FIRST AUTHORISATION

Date of registration: 30 March 2021

10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA: 28 October 2024