IMBRUVICA® 140 mg Hard Capsules

IMBRUVICA® 140 mg, 280 mg, 420 mg, 560 mg Film-Coated Tablets

ABBREVIATED PRESCRIBING INFORMATION BASED ON THE EU SUMMARY OF PRODUCT CHARACTERISTICS

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

ACTIVE INGREDIENT:
Each hard capsule contains 140 mg of ibrutinib.
Each film-coated tablet contains either 140 mg, 280 mg, 420 mg or 560 mg ibrutinib.

INDICATIONS:
IMBRUVICA is indicated for treatment of adult patients: as a single agent for relapsed/refractory mantle cell lymphoma (MCL); as a single agent or in combination with rituximab or obinutuzumab or venetoclax for previously untreated chronic lymphocytic leukaemia (CLL); as a single agent or in combination with bendamustine and rituximab (BR) in CLL after at least one prior therapy; as a single agent for Waldenström's macroglobulinaemia (WM) after at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy; in combination with rituximab for WM.

DOSAGE & ADMINISTRATION:
Adults: Orally, once daily, swallowed whole with water. MCL - 560 mg once daily; CLL and WM as single agent or in combination - 420 mg once daily.
In combination with venetoclax for the treatment of CLL, IMBRUVICA should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of IMBRUVICA plus venetoclax. See the venetoclax Summary of Product Characteristics (SmPC) for full venetoclax dosing information.
In combination with anti-CD20 therapy - administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.
Concomitant strong CYP3A4 inhibitors - reduce IMBRUVICA dose to 140 mg once daily or withhold for up to 7 days.
Concomitant moderate CYP3A4 inhibitors - reduce IMBRUVICA dose to 280 mg once daily.
Withhold IMBRUVICA therapy for any new onset/worsening grade 2 cardiac failure, grade 3 cardiac arrhythmias, grade ≥ 3 non-haematological toxicity, grade ≥ 3 neutropenia with infection or fever, or grade 4 haematological toxicities. Once symptoms of the toxicity have resolved to grade 1 or baseline, follow the dose modification tables for cardiac and non-cardiac events provided in Summary of Product Characteristics (SmPC).
Children: It is not recommended for use as efficacy not established <18 years old. For currently available data in patients with mature B-cell non-Hodgkin lymphoma, please refer to SmPC**.**
Elderly: No dose adjustment required.
Renal impairment: Mild/moderate - no dose adjustment. Severe - no data; consider benefit/risk and monitor closely. No data with dialysis.
Hepatic impairment: Mild (Child-Pugh class A) - 280 mg daily; moderate (Child-Pugh class B) - 140 mg daily; monitor for toxicities. Severe (Child-Pugh class C) - not recommended.
Severe cardiac disease: No clinical data.

CONTRAINDICATIONS:
Hypersensitivity to active substance/excipients.
St. John's Wort preparations.

SPECIAL WARNINGS & PRECAUTIONS:
Bleeding-related events: Minor and major bleeding events reported, some fatal; caution with anticoagulant therapy - do not use concomitantly with warfarin or other vitamin K antagonists. Benefit risk balance of anticoagulant or antiplatelet therapy should be evaluated when co-

administered with IMBRUVICA. Monitor for signs and symptoms of bleeding. Avoid fish oil and vitamin E preparations. Withhold IMBRUVICA ≥ 3 to 7 days pre-/post-surgery.
Leukostasis: Cases reported; consider temporary withhold of IMBRUVICA; monitor closely, give supportive care.
Splenic rupture: Cases of splenic rupture reported following discontinuation of IMBRUVICA treatment. Carefully monitor (e.g. clinical examination, ultrasound) disease status and spleen size 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 seen, some resulting in hospitalisation and death; monitor for fever, abnormal liver function tests, neutropenia and infections and give anti-infective therapy. Consider prophylaxis in patients at increased risk for opportunistic infections. Invasive fungal infections, including Aspergillosis, Cryptococcosis and Pneumocystis jiroveci reported, some with fatal outcomes. Cases of Progressive Multifocal Leukoencephalopathy (PML) including fatal ones reported following ibrutinib use with prior or concomitant immunosuppressive therapy. Consider PML diagnosis in patients with new/worsening neurological/cognitive/behavioral signs/symptoms. If suspected, evaluate and suspend treatment until PML is excluded. If in doubt, refer to a neurologist and consider appropriate diagnostic measures for PML.
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, has occurred in patients treated with IMBRUVICA. Liver function and viral hepatitis status should be assessed before initiating treatment with IMBRUVICA. Patients should be periodically monitored for changes in liver function parameters during treatment. As clinically indicated, viral load and serological testing for infectious hepatitis should be performed per local medical guidelines. For patients diagnosed with hepatic events, consider consulting a liver disease expert for management.
Cytopenias: Treatment-emergent grade 3/4 cytopenias reported; monitor complete blood counts monthly.
Interstitial Lung Disease (ILD): Cases reported; monitor for pulmonary symptoms indicative of ILD; interrupt IMBRUVICA and manage ILD if symptoms develop. If symptoms persist, consider IMBRUVICA risks and benefits; follow dose modification guidelines.
Cardiac arrhythmias and cardiac failure: Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with IMBRUVICA. Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia 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 arrhythmia. 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. For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with IMBRUVICA; alternative treatment may be considered. Temporarily discontinue IMBRUVICA in patients who develop signs and/or symptoms of ventricular tachyarrhythmia; consider alternative to IMBRUVICA when pre-existing atrial fibrillation requiring anticoagulant therapy or high risk of thromboembolic disease; where no suitable alternatives to IMBRUVICA, consider tightly controlled treatment with anticoagulants. Monitor patients 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.
Cerebrovascular accidents: Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported in patients treated with IMBRUVICA, with and without concomitant atrial fibrillation and/or hypertension. Monitor regularly, due to long latency in onset of ischaemic central nervous vascular conditions.

Tumour lysis syndrome: Cases reported; patients with high tumour burden at risk; monitor closely, take precautions.
Non-melanoma skin cancer: Reported more frequently in IMBRUVICA-treated patients than in comparator-treated patients in pooled comparative randomised phase 3 studies. Monitor patients for appearance of non-melanoma skin cancer.
Hypertension: Cases reported; regularly monitor blood pressure and initiate or adjust antihypertensive medication throughout treatment as appropriate.
Haemophagocytic lymphohistiocytosis (HLH): Cases (including fatal) of HLH reported. HLH is a life-threatening syndrome of pathologic immune activation 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.
Drug-drug interactions: Strong/moderate CYP3A4 inhibitors may increase ibrutinib exposure; CYP3A4 inducers may decrease IMBRUVICA exposure. Avoid use of strong CYP3A4 inhibitors and strong/moderate CYP3A4 inducers where possible, if not monitor closely for toxicities/lack of efficacy.
Excipients with known effect: IMBRUVICA film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. IMBRUVICA capsules and film-coated tablets contains less than 1 mmol sodium (23 mg),and is essentially sodium free.

SIDE EFFECTS:
Very common: Pneumonia[#], upper respiratory tract infection, skin infection, neutropenia, thrombocytopenia, lymphocytosis, dizziness, headache, haemorrhage[#], bruising, hypertension, diarrhoea, vomiting, stomatitis, nausea, constipation, dyspepsia, rash, arthralgia, muscle spasms, musculoskeletal pain, pyrexia, oedema peripheral, blood creatinine increased. **Common:** sepsis[#], urinary tract infection, sinusitis, non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, febrile neutropenia, leukocytosis, interstitial lung disease[#], hyperuricaemia, peripheral neuropathy, vision blurred, cardiac failure[#], atrial fibrillation, epistaxis, petechiae, urticaria, erythema, onychoclasis. **Uncommon:** cryptococcal infections, pneumocystis infections[#], aspergillus infections, hepatitis B reactivation[#], tumour lysis syndrome, cerebrovascular accident[#], transient ischaemic attack, ischaemic stroke[#], eye haemorrhage including some cases associated with loss of vision, ventricular tachyarrhythmia[#], cardiac arrest[#], subdural haematoma[#], hepatic failure[#], angioedema, panniculitis, neutrophilic dermatoses. **Rare:** leukostasis syndrome, Stevens-Johnson syndrome.
([#] includes events with fatal outcome)
The overall known safety profile of IMBRUVICA remained consistent with the addition of long-term safety data over 5 years from 1284 patients. No new safety concerns other than an increased prevalence of hypertension.
Refer to the SmPC for other side effects.
Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system to allow for continued monitoring of the benefit/risk balance of the medicinal product.

PREGNANCY:
Not to be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures during and for 3 months after stopping treatment.

LACTATION:
Discontinue breast-feeding during treatment.

INTERACTIONS:
CYP3A4 inhibitors: Strong: Avoid strong CYP3A4 inhibitors where possible or reduce dose of IMBRUVICA to 140 mg for duration of inhibitor use (or withhold IMBRUVICA for ≤ 7 days and

monitor closely; e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, cobicistat, voriconazole and posaconazole. Moderate: Reduce dose of IMBRUVICA to 280 mg for duration of inhibitor use and monitor closely; e.g., erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone. Avoid grapefruit and Seville oranges. Mild: No dose adjustment required; monitor closely.
CYP3A4 inducers: Strong/moderate: Avoid or monitor closely for lack of efficacy; carbamazepine, rifampin, phenytoin. Mild: may be used; monitor for lack of efficacy.
Medicines that increase stomach pH (e.g., proton pump inhibitors) have been used without restrictions in the pivotal clinical studies.
Potential interactions: Narrow therapeutic range oral P-gp or BCRP substrates (e.g., digoxin or methotrexate) should be taken ≥ 6 h before/after IMBRUVICA. Exposure of drugs that undergo BCRP-mediated hepatic efflux (e.g., rosuvastatin) may be increased. In studies of ibrutinib (420 mg) in combination with venetoclax (400 mg) in CLL patients, an increase in venetoclax exposure (approximately 1.8-fold based on AUC) was observed compared with monotherapy data for venetoclax.
Refer to SmPC for full details of interactions.

LEGAL CLASSIFICATION: Medicinal product subject to restricted medical prescription

MARKETING AUTHORISATION NUMBERS:
140 mg capsule: EU/1/14/945/001 (90 hard capsules) and EU/1/14/945/002 (120 hard capsules)
140 mg tablet: EU/1/14/945/007 (28 tablets) and EU/1/14/945/008 (30 tablets)
280 mg tablet: EU/1/14/945/009 (28 tablets) and EU/1/14/945/010 (30 tablets)
420 mg tablet: EU/1/14/945/011 (28 tablets) and EU/1/14/945/005 (30 tablets)
560 mg tablet: EU/1/14/945/012 (28 tablets) and EU/1/14/945/006 (30 tablets)

MARKETING AUTHORISATION HOLDER: Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

Products mentioned in this document may not be registered in all countries. Prescribing Information may vary per country. Health Care Providers must refer to their country prescribing information.

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