World Health Organization

IMBRUVICA® now on the 2021 WHO Model List of Essential Medicines

Experience Real Survival with IMBRUVICA®[1-4]

Real survival is built from real efficacy, real safety and real trust. **Not just predicted, but proven** with real-world experience and up to 8 years of clinical evidence.[1-4]

IMBRUVICA® is the only BTK inhibitor proven to consistently deliver real survival for patients with CLL – making a real impact on real lives, every day.[1-4]

imbruvica F1RST

Live Longer[5-8]*

imbruvica® (ibrutinib)

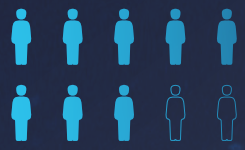
This item is intended for healthcare professionals only.
*vs chemoimmunotherapies (CITs).[5-8]

Date of preparation: February 2022 CP-287081

Real Efficacy:

Only IMBRUVICA® has **overall survival (OS) benefits** supported by 8 years of experience.[4,5]

RESONATE-2



8 out of 10
unfit patients alive

at up to 7 years
(N=269)[5*]

IMBRUVICA® is the only novel targeted therapy to demonstrate OS benefits vs chlorambucil at up to **7 years**[5*]

ECOG 1912

99%
of fit patients alive

at 3 years
(N=529)[6†]

IMBRUVICA® has OS superiority compared with fludarabine, cyclophosphamide and rituximab (FCR) at **3 years** of follow-up[6†]

IMBRUVICA® is the only BTK inhibitor with proven OS benefits from multiple clinical trials[5,6]

*Results from RESONATE-2 trial: A phase III open-label, multicentre, international, randomised study investigating the long-term efficacy and safety of IMBRUVICA® vs chlorambucil in patients with treatment-naive CLL (up to 7 years of follow-up, N=269). 78% of IMBRUVICA® patients were estimated to be alive at 6.5 years. 112 patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0, and 157 had a score of 1-2. OS estimates at 5 years for IMBRUVICA® vs chlorambucil were 83% vs 68%. OS was not captured for chlorambucil arm for patients with disease progression after median 5 years of follow-up. Median OS was not reached with IMBRUVICA® or chlorambucil (HR: 0.514 [95% CI: 0.312–0.848]).[5] †Results from ECOG 1912 trial: A phase III trial comparing IMBRUVICA® and rituximab to FCR in patients (N=529) with previously untreated CLL ≤70 years of age. 63.3% of patients had an ECOG performance-status score of 0. At 3 years, 98.8% of IMBRUVICA® + rituximab patients were alive vs 91.5% with FCR (HR: 0.17 [95% CI: 0.05–0.54] p<0.001).[6]

Real Safety:

Only IMBRUVICA® has the **longest safety follow-up of any BTK inhibitor** with up to **8 years of experience** – providing an expected safety profile that allows patients to continue benefiting from treatment.[4,5]

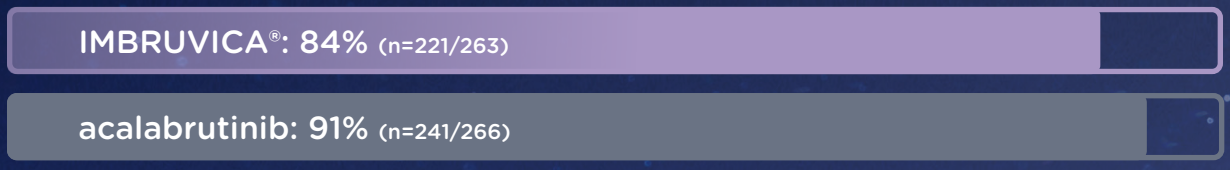
Adverse events (AEs) were primarily Grade 1 and 2[5]

Most AEs were manageable and diminished over time[5]

Dose reductions can effectively manage most AEs, with rates of discontinuation remaining low[5]

In the recent, open-label, head-to-head ELEVATE-RR trial (N=533)**:**[9]

Patients who did not experience atrial fibrillation (AF):



Patients with Grade ≥3 AF:

Less patients experienced Grade ≥ 3 AF with IMBRUVICA®[9]*

All BTK inhibitors require similar management for maximum patient benefit[5,9]

*vs acalabrutinib

Real Trust:

Backed by routine clinical practice in the real world.[1-3]

IBRORS
>8 out of 10

high-risk patients progression-free and alive at up to **2 years** (N=269)[1*]

BiRD
8 out of 10

fit patients alive at **4 years** (N=160)[2†]

FIRE
8 out of 10

relapsed/refractory patients progression-free and alive at **2 years** (n=254)[3‡]

IMBRUVICA® is the only BTK inhibitor with survival benefits proven across multiple real-world studies[1-3]

*91.7% of patients had at least 1 high-risk molecular cytogenetic factor (unmutated immunoglobulin heavy chain variable [IGHV] gene mutation status, *TP53* abnormalities, 11q deletion or complex karyotype). The median progression-free survival (PFS) and overall survival (OS) were not reached, and the estimated PFS at 24 months was 84.5% (73.4–95.6%)[1]. †85.8% of patients had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0–1. At a median follow-up of 24.8 months (95% CI: 21.6–28.0), median OS was not reached.[2] ‡In patients (n=254) who had received 1–2 prior lines of therapy (HR: NR [95% CI: 26.6–NR]).[3]


Deliver Real Survival to your patients.
Prescribe IMBRUVICA® from the start.[1-4,8]
Live Longer[5-8]*
imbruvica®
(ibrutinib)
*vs chemoimmunotherapies (CITs).[5-8]

References:

1. Costa PA, *et al*. Single-agent ibrutinib as first-line treatment for patients with chronic lymphocytic leukemia (CLL) in routine clinical practice in Spain. *Blood*. 2020:136;(Supplement 1):32–33.
2. Janssens A, *et al*. Effectiveness and safety of ibrutinib for chronic lymphocytic leukemia (CLL) in routine clinical practice: interim analysis (IA) of the Belgian ibrutinib real-world data (BiRD) study. Poster presented at the 24th Congress of the European Hematology Association (EHA); 13–16 June 2019; Amsterdam, the Netherlands. #PF384.
3. Dartigeas C, *et al*. French Ibrutinib Observational Study (FIRE): Real-world study of ibrutinib treatment for chronic lymphocytic leukemia (CLL) in France. Poster presented at the 24th Congress of the European Hematology Association (EHA); 13–16 June 2019; Amsterdam, the Netherlands. #PF387.
4. Byrd JC, *et al*. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase 1b/2 PCYC-1102 study. *Clin Cancer Res*. 2020;26(15):3918–3927.
5. Ghia P, *et al*. Ibrutinib treatment in the first-line setting for patients with chronic lymphocytic leukaemia: up to 7 years of follow-up in the RESONATE-2 study. Poster presented at EHA 2021 Virtual Congress; 9–17 June 2021. #EP636.
6. Shanafelt TD, *et al*. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432–443.
7. Munir T, *et al*. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353–1363.
8. IMBRUVICA® Summary of Product Characteristics. 2021.
9. Byrd JC, *et al*. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441–3452.

Prescribing information:

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 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 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 ≥ 3 non haematological toxicity, grade ≥ 3 neutropenia with infection or fever, or grade 4 haematological toxicities. Re initiate when toxicities resolved to grade 1 or baseline. If toxicities reoccur, reduce dose by 140 mg. Consider reducing dose by an additional 140 mg if toxicities persist/recur. Discontinue IMBRUVICA if toxicities persist/recur following two dose reductions. **Children:** Safety/efficacy not established ≤ 18 years old. No data available. **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 arrhythmia and cardiac failure:* Cases of atrial fibrillation and atrial flutter reported particularly in patients with cardiac risk factors/hypertension/acute infections/previous history of atrial fibrillation. Baseline and periodic clinical monitoring for cardiac manifestations, including cardiac arrhythmia and cardiac failure; consider ECG if arrhythmic symptoms or new onset dyspnoea, dizziness or fainting develop; 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, hyperuricaemia, dizziness, headache, haemorrhage#, bruising, hypertension, diarrhoea, vomiting, stomatitis, nausea, constipation, 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#, peripheral neuropathy, vision blurred, cardiac failure#, atrial fibrillation, ventricular tachyarrhythmia#, epistaxis, petechiae, urticaria, erythema, onychoclasis. **Uncommon:** cryptococcal infections, pneumocystis infections#, aspergillus infections, hepatitis B reactivation#, tumour lysis syndrome, cerebrovascular accident#, transient ischaemic attack, eye haemorrhage including some cases associated with loss of vision, subdural haematoma#, hepatic failure#, angioedema, panniculitis, neutrophilic dermatoses. **Rare:** leukostasis syndrome, ischaemic stroke#. **Not known:** 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, nefazodon, 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. 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.

Prescribing information generation date or last revised: 13 January 2022

Based on 20 August 2021 EU Summary of Product Characteristics

Adverse events and product quality complaints should be reported. Healthcare Professionals must refer to their country specific prescribing information for company contact details.

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