Ibrutinib (Imbruvica®) in combination with venetoclax for the treatment of previously untreated chronic lymphocytic leukaemia (CLL)

General information

Drug description	Indication [1]
Ibrutinib (Imbruvica®) is a potent, small-molecule inhibitor of Bruton's tyrosine kinase.	Ibrutinib (Imbruvica®) in combination with venetoclax is indicated for the treatment of adult patients with previously untreated CLL.

Current treatment [2]

- The following first-line treatment recommendations have been made by NICE relevant to this group of CLL/small lymphocytic lymphoma (SLL) patients:
  - Venetoclax is recommended for untreated CLL in adults with a 17p deletion or TP53 mutation when a B-cell receptor pathway inhibitor is unsuitable.
  - Ibrutinib in adults who have a 17p deletion or TP53 mutation and in whom chemo-immunotherapy is unsuitable.
  - Idelalisib monotherapy or in combination with rituximab, are recommended for untreated CLL in adults with a 17p deletion or TP53 mutation.
  - Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated CLL who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if bendamustine-based therapy is not suitable.
  - Bendamustine is recommended as an option for the first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
  - Rituximab in combination with fludarabine and cyclophosphamide is recommended as an option for the first-line treatment of CLL in people for whom fludarabine in combination with cyclophosphamide is considered appropriate. Rituximab in combination with chemotherapy agents other than fludarabine and cyclophosphamide is not recommended for the first-line treatment of CLL.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 23 June 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imbruvica®. The CHMP adopted an extension to an existing indication to include its use in combination with venetoclax: ❖ Imbruvica® as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated CLL. **Other indications**: Imbruvica® is indicated: ❖ as a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). ❖ as a single agent or in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy. ❖ 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. Imbruvica® in combination with rituximab is indicated for the treatment of adult patients with WM.	**Approval status for this indication**: not approved **Other indications**: Imbruvica® is indicated for the treatment of: ❖ adult patients with MCL who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. ❖ adult patients with CLL/SLL. ❖ adult patients with CLL/SLL with 17p deletion. ❖ adult patients with WM. ❖ adult patients with marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy. This indication is approved under accelerated approval based on overall response rate. ❖ adult and paediatric patients age 1 year and older with chronic graft versus host disease after failure of one or more lines of systemic therapy. According to the FDA label information, for CLL/SLL, Imbruvica® can be administered as a single agent, in combination with rituximab or obinutuzumab, or in combination with bendamustine and rituximab.

Costs

28 Imbruvica® tablets 420 mg = € 4,797.37 (ex-factory price) [4].

Special warnings and precautions for use [5]

- **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.
- Warfarin or other vitamin K antagonists should not be administered concomitantly with Imbruvica®.
- Use of either anticoagulants or medicinal products that inhibit platelet function (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 held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied.

❖ **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 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, 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, abnormal liver function tests, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections.
- Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib. Reported cases of invasive fungal infections have been associated with fatal outcomes.
- Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy.
- Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML including MRI scan preferably with contrast, cerebrospinal fluid testing for JC Viral DNA and repeat neurological assessments should be considered.

❖ **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 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 arrhythmias and cardiac failure**
- Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with Imbruvica®. Patients with advanced age, 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.

- In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, Imbruvica® should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.
- In patients with pre-existing 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.

❖ **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. Among cases with reported latency, the initiation of treatment with Imbruvica® to the onset of ischaemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases) emphasising the need for regular monitoring of patients.

❖ **Tumour lysis syndrome**
- Tumour lysis syndrome has been reported with Imbruvica® therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.

❖ **Non-melanoma skin cancer**
- Non-melanoma skin cancers were reported more frequently in patients treated with Imbruvica® than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.

❖ **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.

❖ **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 CYP3A4 inhibitors and strong or moderate CYP3A4 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. 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®.

❖ **Excipients with known effect**
- Each capsule contains less than 1 mmol sodium (23 mg), and is essentially sodium-free.

Study characteristics [6-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
GLOW, CLL3011 NCT03462719	211 1:1	3 cycles of ibrutinib lead-in at 420 mg once	six 28-day cycles of 1000 mg/day of IV	PFS (assessed by an independent	ongoing[2], randomised, open-label, phase 3 trial	-	Janssen Research & Development,	[8]

[2] The GLOW trial is currently ongoing; estimated study completion date is 04/2024.

		daily, followed by 12 cycles of ibrutinib-venetoclax[1]	obinutuzumab on days 1 (or 100 mg/day on day 1 and 900 mg/day on day 2), 8, and 15 of cycle 1 and day 1 of cycles 2 to 6) plus chlorambucil per label (0.5mg/kg body weight on days 1 and 15 of each cycle)	review committee)			LLC, and Pharmacyclics	

Efficacy (I vs. C)	**Safety** (I vs. C)
Median follow-up at primary analysis: 27.7 months (range, 1.7-33.8) **PFS**: significantly longer with I vs. C, HR 0.216; 95% CI, 0.131-0.357; p=0.001 **Median IRC-assessed PFS:** not reached (95% CI, 31.2-not reached) vs. 21.0 months (95% CI,16.6-24.7) **Estimated 24-month PFS rates**: 84.4% vs. 44.1% **Estimated 30-month PFS rates** (with an additional 6 months of study follow-up: median 34.1 months): 80.5% vs. 35.8% **Best uMRD rate in bone marrow** by next-generation sequencing at time of primary analysis: significantly higher for patients in I vs. C: 55.7% vs. 21.0%; p=0.001 **CR rate by IRC**: significantly higher rate in I than in C: 38.7% vs. 11.4%; p=0.001 **CR rate investigator-assessed**: 45.3% vs. 13.3% **ORR by IRC**: 86.8% vs. 84.8% **24-month duration of response rates**: 90% vs. 41% **Number of deaths at the time of primary analysis**: 11 vs. 12 with no difference in OS between arms; HR 1.048; 95% CI, 0.454-2.419 **Occurrence of Richter's transformation**[3] [10]: 2.8% vs. 1.9% **Number of patients requiring subsequent anticancer therapy**: 4 vs. 27	**AEs grade ≥3 or greater:** n=80/106 (75.5%) vs. n=73/105 (69.5%) **Any SAEs:** n=49/106 (46.2%) vs. n=29/105 (27.6%) **Treatment-emergent deaths:** n=7/106 (6.6%) vs. n=2/105 (1.9%) **Number of deaths with an additional 6 months of study follow-up (median 34.1 months)**: 0 vs. 4 **Total number of deaths**: 11 vs. 16 deaths; HR 0.760; 95% CI, 0.352-1.642 **Discontinuation due to AEs:** 10.4% vs. 1.9%

ESMO-MCBS version 1.1 [11, 12][4]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because the primary endpoint PFS was not reached.											

Risk of bias (RCT) [13]

[1] Venetoclax was initiated in cycle 4 with dose ramp-up per label over 5 weeks (20, 50, 100, 200, and 400 mg/day) and continued at 400mg/day dose from cycle 5 onward. Ibrutinib and Venetoclax were administered on 28-day cycles.

[3] Richter's Syndrome (also known as Richter's Transformation) is a rare complication of CLL and/or SLL. It is characterised by the sudden transformation of the CLL/SLL into a significantly more aggressive form of large cell lymphoma. Richter's Syndrome occurs in approx. 2-10% of all CLL/SLL patients during the course of their disease.

[4] Disclaimer: Though not finally validated, but feasibility tested in [12], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	no, open-label	unclear[5]	yes[6]	unclear
					First published: 07/2022 Last updated: 11/2022

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLL=chronic lymphocytic leukaemia, CR=complete response, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HLH= Haemophagocytic lymphohistiocytosis, HR=hazard ratio, I=intervention, ILD=Interstitial Lung Disease Int.=intention, MCL=mantle cell lymphoma, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PML=progressive multifocal leukoencephalopathy, QoL=quality of life, SAE=serious adverse event, SLL=small lymphocytic lymphoma, ST=standard treatment, TLS=tumor lysis syndrome, uMRD=undetectable minimal residual disease, WM=Waldenström's macroglobulinaemia

References:

1. European Medicines Agency (EMA). Medicines. Imbruvica. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imbruvica-1].
2. National Institute for Health Research (NIHR). Ibrutinib in combination with venetoclax for chronic lymphocytic leukaemia or small lymphocytic lymphoma – first line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/24051-Ibrutinib-Venetoclax-for-CLL-or-SLL-V1.0-AUG2020-NONCONF.pdf].
3. U.S. Food and Drug Administration (FDA). Imbruvica. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205552s035,215063s011lbl.pdf].
4. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
5. European Medicines Agency (EMA). Imbruvica: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf].
6. Protocol for: Arnon P. Kater, Carolyn Owen, Carol Moreno, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence.
7. Supplement to: Arnon P. Kater, Carolyn Owen, Carol Moreno, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence.
8. Kater A, Owen C, Moreno C, et al., for the GLOW Investigators. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evid 2022; 1 (7). [Available from: https://doi.org/10.1056/EVIDoa2200006].
9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of the Combination of Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab for the First-line Treatment of Participants With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). [Available from: https://clinicaltrials.gov/ct2/show/NCT03462719].
10. Leukaemia Foundation. Richter's Syndrome. [Available from: https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/chronic-lymphocytic-leukaemia/richters-syndrome/].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Kiesewetter B , Cherny NI, Boissel N, et al. EHA evaluation of the ESMO—Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. ESMO Open 2020;5.

[5] The GLOW trial is currently ongoing.

[6] The study was sponsored and designed by Janssen Research & Development, LLC, with input from investigators. Data were collected by investigators under the oversight of an independent data monitoring committee and were confirmed and analysed by the sponsor. The manuscript was written based on author guidance with the assistance of a medical writer supported by the sponsor, and all authors critically reviewed drafts and approved the manuscript for publication.

13. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].