Ibrutinib Therapy CLL/ Waldenström's Macroglobulinaemia

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As a single agent for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.	C91	00296a	CDS
As a single agent for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy.	C91	00296b	CDS
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.	C88	00296c	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ibrutinib is taken orally, once daily and treatment is continued until disease progression or unacceptable toxicity develops.

Drug	Indication	Dose	Route	Cycle
Ibrutinib	**CLL or WM**	420mg daily	PO	Continuous
Ibrutinib should be taken with a glass of water approximately at the same time each day. Capsules should be swallowed whole with water and should not be opened, broken or chewed. Ibrutinib must not be taken with grapefruit juice or Seville oranges.				
If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.				
Ibrutinib is available as 140mg capsules				

ELIGIBILITY:

- ECOG 0-2
- CLL - First line
  - Patients who have confirmed presence of 17p deletion or TP53 mutation.
- CLL – Second line.
  - Patients must have received at least one prior therapy for CLL
- Waldenström's macroglobulinaemia (WM) - Patients who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy

EXCLUSIONS:

- Hypersensitivity to ibrutinib or any of the excipients
- Severe hepatic impairment (Child-Pugh score Class C)
- Severe cardiovascular disease
- Pregnancy
- Breast feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist experienced in the treatment of haematological malignancies

TESTS:

Baseline tests:

- Blood, renal and liver profile
- DCT, coagulation screen
- ECG
- Virology screen - Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV.
  *Hepatitis B reactivation: See adverse events/Regimen specific complications

Regular tests:

- Blood, renal and liver profile monthly for first three months and then three monthly

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Table 1: Recommended dose modifications for ibrutinib after recovery from non-cardiac adverse reactions

Toxicity Occurrence	CLL/WM dose modification after recovery
First	Restart at 420mg daily
Second	Restart at 280mg daily
Third	Restart at 140mg daily
Fourth	Discontinue ibrutinib

* When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If toxicity reoccurs, reduce daily dose by 140 mg

Haematological:

Table 2: Dose modifications of ibrutinib in haematological toxicity

ANC (x10^9/l)		Platelets (x10^9/l)	Dose
<1.0 with infection or fever			Withhold treatment until resolved to Grade 1 or baseline (recovery). Treatment may be reinitiated following the recommended dose modifications in Table 1 above
<0.5	or	<25	

Non-haematological toxicity:

- Ibrutinib should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity
- Once the toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, again following the recommended dose modifications in Table 1 above.

Cardiac Toxicity

- Ibrutinib should be withheld for any new onset or worsening grade 2 cardiac failure or grade 3 cardiac arrhythmias
- Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), resume therapy at the recommended dose as per table 3 below

Table 3: Recommended dose modifications for ibrutinib after recovery from cardiac adverse reactions

Events	Toxicity recurrence	CLL/WM dose modification after recovery
Grade 2 cardiac failure	First	Restart at 280 mg daily
	Second	Restart at 140 mg daily
	Third	Discontinue treatment
Grade 3 cardiac arrhythmias	First	Restart at 280 mg daily[a]
	Second	Discontinue treatment
Grade 3 or 4 cardiac failure OR Grade 4 cardiac arrhythmias	First	Discontinue treatment

[a]Evaluate the risk-benefit before resuming treatment

Renal and Hepatic Impairment:

Table 4. Recommended dose modification for ibrutinib in patients with renal or hepatic impairment

<table>
<tr><th>Renal impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td rowspan="5">No specific clinical studies have been conducted in patients with renal impairment.
No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl>30mL/min).

Hydration should be maintained and serum creatinine levels monitored periodically.

Ibrutinib should be administered to patients with severe renal impairment (CrCl<30mL/min) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity.
There are no data in patients with severe renal impairment or patients on dialysis</td><td colspan="2">Ibrutinib is metabolised in the liver. When using ibrutinib in patients with mild or moderate hepatic impairment, monitor patients for signs of ibrutinib toxicity and follow dose modification guidance as needed.</td></tr>
<tr><td>Liver Impairment Status</td><td>Recommended dose</td></tr>
<tr><td>Mild (Child-Pugh class A)</td><td>280mg daily</td></tr>
<tr><td>Moderate (Child-Pugh class B)</td><td>140 mg daily</td></tr>
<tr><td>Severe (Child-Pugh class C)</td><td>Not recommended</td></tr>
</table>

Co-administration with moderate and strong CYP3A4 inhibitors

Table 5: Recommended dose modifications for ibrutinib when administered with moderate or strong CYP3A4 inhibitors

Level of CYP3A4 Inhibition	Dose
Moderate	Reduce to 280mg once daily
Strong	Reduce to 140mg once daily or withhold for up to 7 days

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to low (**Refer to local policy).**

PREMEDICATIONS: Not usually required.

OTHER SUPPORTIVE CARE:

- Medication may be required for the treatment of diarrhoea **(Refer to local policy).**
- Tumour lysis syndrome prophylaxis **(Refer to local policy**).
- Consider PJP prophylaxis in heavily pretreated patients **(Refer to local policy**).
- Women of childbearing potential must use a highly effective method of contraception while taking ibrutinib and for three months after stopping treatment.
- It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Bleeding related events:** There have been reports of haemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor haemorrhagic events such as contusion, epistaxis, and petechiae; and major haemorrhagic events including gastrointestinal bleeding, intracranial haemorrhage, and haematuria. ***Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib*.** Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- **Leukostasis:** A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily holding ibrutinib. Patients should be closely monitored. Supportive care including hydration and/or cytoreduction should be administered as indicated.
- **Splenic rupture:** Cases of splenic rupture have been reported following discontinuation of ibrutinib treatment. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when ibrutinib 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.
- **Cytopenias:** Treatment-associated grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Monitor blood counts monthly for the first 6 months and then at least 3 monthly
- **Infections:** Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalization and death, especially in patients who were neutropenic. Patients should be monitored for fever, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated.
- **Progressive multifocal leukoencephalopathy (PML)**: cases including fatal ones have been reported following the use of ibrutinib within the context of a prior or concomitant immunosuppressive therapy.
- **Cardiac arrhythmias and cardiac failure**: Fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with ibrutinib. 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 ibrutinib. 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 ibrutinib; alternative treatment may be considered. In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, ibrutinib 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 ibrutinib should be considered. In patients who develop atrial fibrillation on therapy with ibrutinib a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are non-suitable, tightly controlled treatment with anticoagulants should be considered. Patients should be monitored for signs and symptoms of cardiac failure during ibrutinib treatment. In some of these cases cardiac failure resolved or improved after ibrutinib withdrawal or dose reduction.

- **Tumour lysis syndrome**: Tumour lysis syndrome has been reported with ibrutinib therapy. Patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Monitor patients closely and take appropriate precautions.
- **Effects on the QT interval:** In a phase 2 study, ECG evaluations showed ibrutinib produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding are not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).
- **Second Primary Malignancies:** Other malignancies (5 to 10%) including carcinomas (1 to 3%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (4 to 8%).
- **Non-melanoma skin cancer:** Non-melanoma skin cancers were reported more frequently in patients treated with Ibrutinib than in patients treated with comparators in pooled comparative randomised phase 3 studies. Monitor patients for the appearance of non-melanoma skin cancer.
- **Hepatitis B reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.
- **Hypertension:** Hypertension has occurred in patients treated with ibrutinib. Regularly monitor blood pressure in patients treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.
- **Interstitial Lung Disease (ILD)**: Cases of ILD have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt treatment and manage ILD appropriately. If symptoms persist, consider the risks and benefits of treatment and follow the dose modification guidelines.
- **Cerebrovascular accidents:** Cases of cerebrovascular accident, transient ischaemic attack and ischaemic stroke including fatalities have been reported with the use of ibrutinib, with and without concomitant atrial fibrillation and/or hypertension. Latency from the initiation of treatment with ibrutinib 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.

DRUG INTERACTIONS:

Moderate and strong CYP3A4 inhibitors

- Co-administration of moderate or strong CYP3A4 inhibitors with ibrutinib may lead to increased ibrutinib exposure and consequently a higher risk for toxicity.
- Concomitant use of ibrutinib with strong or moderate CYP3A4 inhibitors/inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits

clearly outweigh the potential risks. Patients should be closely monitored for signs of ibrutinib toxicity if a CYP3A4 inhibitor must be used.

CYP3A4 inducers

- Co-administration of CYP3A4 inducers may lead to decreased ibrutinib exposure and reduced efficacy. Concomitant use of ibrutinib with strong or moderate CYP3A4 inducers should be avoided whenever possible and co-administration should only be considered when the potential benefits outweigh the potential risks. If a CYP3A4 inducer must be used, monitor patients for signs of ibrutinib lack of efficacy.
- Ibrutinib is a P-gp inhibitor *in vitro*. No clinical data are available on this interaction, therefore, ibrutinib may inhibit intestinal P-gp after a therapeutic dose. To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Burger, J. A., A. Tedeschi, P. M. Barr, et al. 2015. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med 373(25):2425-2437.
3. MHRA Drug Safety Update Volume 11 Issue 1 August 2017. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/637656/DSU-August_PDF.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. HPRA Direct Healthcare Professional Communication. Imbruvica® (ibrutinib): New risk minimisation measures, including dose modification recommendations, due to the increased risk for serious cardiac events. Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-imbruvica-(ibrutinib).pdf?sfvrsn=0
6. Ibrutinib (IMBRUVICA®) Summary of product characteristics EMA. Accessed Oct 2022. https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	19/07/16		Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
2	22/01/17	Eligibility criteria for use in second line CLL reviewed.	Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
3	23/08/2017	Update of Adverse Reactions in terms of ventricular arrhythmia as per safety update. Updated with new NCCP regimen template	Prof. Elisabeth Vandenberghe, Dr. Patrick Thornton
4	25/11/2019	Updated adverse events and drug interactions.	Dr. Patrick Thornton
5	28/11/2022	Reviewed. Updated adverse events section. Updated dose modifications for cardiac toxicity as per DHPC from HPRA Nov 2022.	Prof. Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.