Indication	Monotherapy for the treatment of CLL which has a 17p deletion or TP53 mutation, patients should have not received any previous BTK inhibitor therapy unless 1st line acalabrutinib or 1st line zanubrutinib has been stopped solely for dose limiting toxicity and in the clear absence of disease progression. Monotherapy for the treatment of previously treated CLL, patients should have not received any previous BTK inhibitor therapy unless: acalabrutinib or zanubrutinib has been stopped solely for dose limiting toxicity and in the clear absence of disease progression. or the patient received 1st line ibrutinib plus venetoclax and was in response to treatment on completion and this regimen is the first BTK inhibitor to be prescribed since relapse. For Relapsed or Refractory Mantle Cell Lymphoma (MCL) in patients who have received only 1 prior line of rituximab-containing chemotherapy ONLY or the patient has received ≥2 lines of therapy as long as 2nd line therapy was commenced before January 2018, the time at which NICE issued its guidance restricting use to 2nd line therapy only. **NB there are 2 dosing schedules one for CLL and one for MCL.**
Treatment Intent	Disease Modification
Frequency and number of cycles	Repeat every 28 days. **Schedule 1** for the treatment of CLL **Schedule 2** for the treatment of MCL Continuously until disease progression or unacceptable toxicity or patient choice to stop treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **ECG baseline.** Further cardiac evaluation including an ECHO should be considered in patients with cardiac risk factors or previous anthracycline therapy. • FBC, LFTs, creatinine, urea and electrolytes should be measured before each cycle. • **BP** to be monitored every cycle. • Proceed with next cycle if ANC >/= 0.5 x 10^9/L and platelets >/= 25 x 10^9/L. If counts below these check with consultant. • **Cardiac arrhythmia and cardiac failure:** ○ Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia and cardiac failure have been reported in patients treated with ibrutinib. Periodically monitor all patients clinically for cardiac manifestations including arrhythmia and cardiac failure. 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. • **Renal impairment:** • No dose adjustment for patients with CrCl>30ml/min. No data in patients with CrCl<30ml/min, use only if benefit outweighs risk. Monitor closely for signs of toxicity.

	• **Hepatic impairment:** Ibrutinib is metabolised in the liver. 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 toxicity and follow dose modification guidance as needed (see SPC). It is not recommended to administer Ibrutinib to patients with severe hepatic impairment (Child-Pugh class C). • Monitor patient closely for any signs and symptoms of bleeding. Treatment should be held 3 to 7 days pre and post-surgery dependant on type of surgery. • **Interstitial Lung Disease (ILD)** • Cases of ILD have been reported in some patients. 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 (see SPC). • Cases of invasive fungal infections, including cases of Aspergillosis, Cryptococcosis and Pneumocystis jiroveci infections have been reported following the use of ibrutinib. • **Splenic rupture** • Cases of splenic rupture have been reported following discontinuation of ibrutinib. Disease status and spleen size should be carefully monitored (e.g. clinical examination, ultrasound) when treatment is interrupted/discontinued. Patients who develop left upper abdominal or shoulder tip pain should be assessed and splenic rupture should be considered. • **Dose Modifications**: • Ibrutinib should be withheld if neutrophils < 1.0 x 10^9/l with infection or fever, or any grade 4 haematological toxicity (e.g. neutrophils < 0.5 x10^9/l or platelets < 25 x 10^9/l). Withhold ibrutinib for any new onset or worsening grade >/=3 non-haematological toxicity. Once toxicity has resolved to Grade 1 or baseline, ibrutinib may be re-started, following table 1 below. If the toxicity reoccurs, the once daily dose should be reduced by 140 mg. A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product. • **Common drug interactions: (for comprehensive list refer to BNF/SPC)** o Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. o Patient receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising. Ibrutinib should be withheld in the event of any bleeding events. o Ibrutinib is metabolised by CYP 3A. Avoid concomitant use of strong (ketoconazole, clarithromycin, itraconazole and ritonavir) or moderate (fluconazole, erythromycin, amprenavir, aprepitant,and atazanavir) CYP3A inhibitors. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the dose to 140 mg for the duration of the inhibitor use or withhold ibrutinib temporarily (for 7 days or less). If a moderate CYP3A4 inhibitor is indicated, reduce ibrutinib dose to 280 mg for the duration of the inhibitor use. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid moderate or strong inducers (e.g. carbamazepine, rifampicin, phenytoin, and St. John's Wort).

	○ To minimise the potential for an interaction in the GI tract, oral narrow therapeutic range, P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. ○ Do not take with grapefruit juice or Seville oranges. ○ Supplements such as fish oil and vitamin E preparations should be avoided. ○ Patients should be made aware that ibrutinib may affect their ability to drive and use machines. • **Missed dose:** If a dose is missed it should be taken as soon as possible on the same day and the patient should return to the normal schedule the following day. • **For oral self-administration:** refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.
References	KMCC proforma HAEM-CLL-029 v7 SPC accessed online 03.11.2023 CDF list V1.279 accessed online 03.11.2023

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1

Recommended dose modifications are described below:

Toxicity Occurrence	CLL dose modification after recovery	MCL dose modification after recovery
First	Restart at 420mg daily	Restart at 560mg daily
Second	Restart at 280mg daily	Restart at 420mg daily
Third	Restart at 140mg daily	Restart at 280mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Schedule 1 for the treatment of CLL (HAEM-CLL-029)

Repeat every 28 days

Day	Drug	Dose	Route	Administration
1	**IBRUTINIB**	**420mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **420mg, 280mg and 140mg** tablets.
	Allopurinol	300mg	PO	OD for 4 weeks. **Cycle one only**
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Co-trimoxazole	480mg	PO	BD on a Monday Wednesday and Friday only.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			

Schedule 2 for the treatment of Mantle Cell Lymphoma (HAEM-NHL-074)

Repeat every 28 days

Day	Drug	Dose	Route	Administration
1	**IBRUTINIB**	**560mg**	PO	To be taken once a day at approximately the same time each day. Swallow whole with water. Available as **560mg, 420mg, 280mg and 140mg** tablets.
	Allopurinol	300mg	PO	OD for 4 weeks. **Cycle one only**
	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD
	Co-trimoxazole	480mg	PO	BD on a Monday Wednesday and Friday only.
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			