Indication	Monotherapy for the treatment of patients with previously treated Waldenstrom's macroglobulinaemia, who would otherwise be next treated with bendamustine plus rituximab. NB Patients must be treatment naïve to a Bruton's kinase inhibitor unless received zanubrutinib via an early access scheme for previously treated Waldenstrom's macroglobulinaemia or the patient previously commenced ibrutinib for previously treated Waldenstrom's macroglobulinaemia which was discontinued solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression.
Treatment Intent	Disease modification.
Frequency and number of cycles	Repeat every 28 days continuous cycle Treatment should continue until disease progression, unacceptable toxicity or patient choice. A formal medical review should take place by the end of the first 8 weeks of treatment to establish if treatment should continue.
Monitoring Parameters pre-treatment	• Check virology status before initiating treatment. • ECG baseline and as clinically indicated. • Monitor FBCs, LFTs and U&Es at baseline and at each cycle. • **Hepatic impairment:** No recommended dose reduction in mild to moderate hepatic impairment. In severe hepatic impairment dose reduce to 80mg BD. • **Renal impairment:** No dose modification is recommended in patients with mild to moderate renal impairment (CrCl>/=30 ml/min). Patients with severe renal impairment (CrCl <30 ml/min) or on dialysis should be monitored for adverse reactions. • **Management of adverse reactions and dose adjustments:** • **Dose Modification:** Dosing delay or discontinuation may be required based on individual safety and tolerability; see Table 1. • **Haemorrhage:** Fatal and serious haemorrhagic events have occurred in patients with haematological malignancies treated with zanubrutinib, both with or without concomitant antiplatelet or anticoagulation therapy. Patients should be monitored for signs and symptoms of bleeding. Consider the benefit-risk of withholding treatment for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. • **Cardiac Arrhythmias:** Monitor for signs and symptoms of atrial fibrillation and atrial flutter and manage as appropriate. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk monitor closely. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** • Concomitant use of strong (e.g. ketoconazole, itraconazole, clarithromycin) and moderate (fluconazole, erythromycin, amprenavir, aprepitant and atazanavir) CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, dose reduce to **80mg OD** and if a moderate CYP3A4 inhibitor cannot be avoided, dose reduce to **80mg BD.** If the CYP3A4 inhibitor is discontinued, the zanubrutinib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor • Concomitant use with moderate or strong CYP3A inducers should be avoided. • Co-administration with antiplatelet or anticoagulant medications may increase the risk of haemorrhage. Monitor at risk patients closely for signs and symptoms of bleeding. • Warfarin or other vitamin K antagonists should not be administered concomitantly with zanubrutinib. • The coadministration of oral P-gp substrates with a narrow therapeutic index (e.g. digoxin) should be done with caution as zanubrutinib may increase their concentrations. • Do not take with grapefruit juice or Seville oranges.

	• **Missed dose:** If a dose is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. • **Driving:** Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213217s005lbl.pdf https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf SPC accessed online 31.10.2022

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

Table 1: Recommended Dosage Modification for Adverse Reaction

Event	**Adverse reaction occurrence**	**Dosage Modification** (Starting Dose: 160 mg twice daily or 320 mg once daily)
Haematological and Non-Haematological toxicities		
Grade 3 febrile neutropenia Grade 3 thrombocytopenia with significant bleeding	First	Interrupt treatment Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 160 mg twice daily or 320 mg once daily. *
Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days) Grade 3 or 4 non-haematological toxicities *	Second	Interrupt treatment Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg twice daily or 160 mg once daily.
	Third	Interrupt treatment Once toxicity has resolved to Grade 1 or lower or baseline: Resume at 80 mg once daily
	Fourth	Discontinue treatment

* Evaluate the benefit-risk before resuming treatment at the same dose for a Grade 4 non-haematological toxicity.

Repeat every 28 days continuous cycle

TTO	Drug	Dose	Route	Directions
	ZANUBRUTINIB	**320mg**	PO	160mg BD Or 320mg OD Swallow whole, do not open, crush or chew the capsules. Available as 80mg capsules
	Co-trimoxazole	480mg	PO	BD on a Monday, Wednesday and Friday only.
	Aciclovir	400mg	PO	BD
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			