Indication	Monotherapy for the treatment of: • previously treated Waldenstrom's macroglobulinaemia, in patients who would otherwise be next treated with bendamustine plus rituximab. 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. • previously **untreated** chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) which has a 17p deletion and/or TP53 mutation. The patient must have not had previous systemic therapy for CLL/SLL unless 1st line zanubrutinib was previously commenced via a BeiGene early access scheme or 1st line acalabrutinib or 1st line ibrutinib has had to be stopped due to dose-limiting toxicity and in the clear absence of disease progression. • previously **untreated** chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) which **does not** have a 17p deletion or a TP53 mutation in patients who would otherwise have been considered as unsuitable for treatment with the combination of fludarabine, cyclophosphamide and rituximab (FCR) or the combination of bendamustine and rituximab (BR). The patient must have not received any previous systemic therapy for CLL/SLL unless 1st line zanubrutinib was previously commenced via a BeiGene early access scheme or 1st line acalabrutinib has had to be stopped solely due to dose-limiting toxicity and in the clear absence of disease progression. • previously **treated** chronic lymphatic leukaemia (CLL) with or without a 17p deletion and/or TP53 mutation. Patients must be treatment naïve to a Bruton's kinase inhibitor or the patient previously commenced ibrutinib or acalabrutinib monotherapy for previously treated CLL/SLL and the ibrutinib or acalabrutinib had to be discontinued solely due to dose-limiting toxicity and in the clear absence of disease progression or the patient has previously been treated with the 1st line combination of ibrutinib plus venetoclax and was still in response on completion of treatment but has since relapsed. • Previously **treated** marginal zone lymphoma (MZL) treated with at least 1 prior anti-CD20-based therapy. Patients must be treatment naïve to a Bruton's kinase inhibitor or have been treated with zanubrutinib via a company access scheme. • For the treatment of relapsed/refractory mantle cell lymphoma (MCL) in patients who have received **only** 1 prior line of systemic therapy which contained rituximab. Patients must have not received prior therapy with a BTK inhibitor (ibrutinib or zanubrutinib or another BTK inhibitor) unless the patient has either received zanubrutinib via a company early access scheme or the patient has received ibrutinib which has had to be stopped due to 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	• **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 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 and monitor patients closely. • **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. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with zanubrutinib. 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, acute infections and patients >/=65 years may be at increased risk monitor closely. • **Tumour lysis syndrome** has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for chronic lymphocytic leukaemia (CLL). Assess relevant risks (e.g., high tumour burden or blood uric acid level) and take appropriate precautions. Monitor patients closely and treat as appropriate. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • Concomitant use of strong (e.g. posaconazole, voriconazole, ketoconazole, itraconazole, clarithromycin) and moderate (fluconazole, erythromycin, ciprofloxacin, 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 strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided. If a moderate CYP3A inducer (e.g. bosentan, efavirenz, etravirine, modafinil) cannot be avoided increase dose to **320mg BD.** • 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. A double dose should not be taken to make up for a missed dose. • **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	MULTI-031 V2 CDF list V1.368

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 Grade 4 neutropenia (lasting more than 10 consecutive days) Grade 4 thrombocytopenia (lasting more than 10 consecutive days) >/= Grade 3 non-haematological toxicities	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.
	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

Repeat every 28 days continuous cycle

TTO	Drug	Dose	Route	Directions
Day 1	**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
	Allopurinol	300mg	PO	OD **Cycle 1 only.**
	Consider antifungal prophylaxis only in patients with additional risk factors being aware of drug interactions with CYP3A inhibitors			