Zanubrutinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
As monotherapy for the treatment of adult patients with Waldenström's macroglobulinaemia (WM), who have received at least one prior therapy or as first line treatment for patients unsuitable for chemo-immunotherapy	C88	00708a	CDS 01/05/2022
As monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia (CLL), who are treatment naïve and have del(17p) and/or TP53-mutated disease	C91	00708b	CDS 01/09/2023
As monotherapy for the treatment of adult patients with CLL, who have relapsed and/or refractory disease following at least one line of prior therapy	C91	00708c	CDS 01/09/2023

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 patient's individual clinical circumstances.

Zanubrutinib is taken orally and should be continued until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Zanubrutinib	320mg once daily (or 160mg twice daily)	PO	Continuous
Zanubrutinib can be taken with or without food. Capsules should be swallowed whole with water and should not be opened, broken or chewed.			
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.			

ELIGIBILITY:

- Indications as above
- ECOG performance status 0–2

EXCLUSIONS:

- Known hypersensitivity to zanubrutinib or any of its listed excipients
- Clinically significant cardiovascular disease (i.e., uncontrolled arrhythmia, class 3/4 congestive heart failure as defined by the NYHA)
- Concomitant warfarin, vitamin K antagonist
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DCT, coagulation screen
- Virology screen: HIV, Hep B and C. Patients should be tested for both HBsAg and HBcoreAb as per local policy
- ECG
- A pregnancy test should be performed on all women of reproductive potential prior to initiating treatment

Regular tests:

- FBC, renal and liver profile monthly for first three months and then, three monthly
- ECG where clinically indicated

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.
- Recommended dose modifications of zanubrutinib for Grade 3 or greater adverse reactions are provided in Table 2.
  - Asymptomatic lymphocytosis should not be regarded as an adverse reaction and these patients should continue taking zanubrutinib.
- Recommended dose modifications for use with CYP3A inhibitors or inducers are provided in Table 3.

Renal and Hepatic Impairment:

Table 1: Dose modification of zanubrutinib in renal and hepatic impairment

Renal impairment		**Hepatic impairment**	
Mild / Moderate (CrCl ≥ 30 ml/min)	No dose adjustment necessary	**Mild / Moderate**	No dose adjustment necessary.
Severe (CrCl <30ml/ min) / on dialysis	Limited data available – monitor for adverse reactions	**Severe**	Safety in these patients has not been evaluated. Monitor closely for adverse events. Recommended dose is 80mg twice daily.

Management of adverse events:

Table 2: Dose modifications of zanubrutinib for adverse events

Adverse reaction	Adverse reaction occurrence	Dose modification (starting dose: 320 mg once daily or 160 mg twice daily)
• ≥Grade 3 non-haematological toxicities • Grade 3 febrile neutropenia • Grade 3 thrombocytopenia with significant bleeding • Grade 4 neutropenia (lasting > 10 consecutive days) • Grade 4 thrombocytopenia (lasting >10 consecutive days)	First	Interrupt zanubrutinib. Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 320 mg once daily or 160 mg twice daily
	Second	Interrupt zanubrutinib. Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 160 mg once daily or 80 mg twice daily
	Third	Interrupt zanubrutinib. Once toxicity has resolved to ≤Grade 1 or baseline: Resume at 80 mg once daily
	Fourth	Discontinue zanubrutinib

Dose modifications for concomitant therapy with CYP3A inhibitors or inducers:

Table 3: Dose modifications of zanubrutinib when co-administered with CYP3A inhibitors or inducers

CYP3A	Co-administered medicinal product	Recommended dose
Inhibition	Strong / Moderate CYP3A inhibitors	80 mg once daily
Induction	Strong / Moderate CYP3A inductions	Avoid concomitant use; Consider alternative agents with less CYP3A induction

SUPPORTIVE CARE:

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

PREMEDICATIONS: None required

OTHER SUPPORTIVE CARE:

- Women of childbearing potential must use highly effective contraceptive measures while taking zanubrutinib and for up to 1 month after stopping treatment.
- It is currently unknown whether zanubrutinib may reduce the effectiveness of hormonal contraceptives and therefore, women using hormonal contraceptives should add a barrier method.
- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- Consider anti-microbial prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Zanubrutinib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Bleeding related events:** Serious and fatal haemorrhagic events have occurred in patients treated with zanubrutinib monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal haemorrhage, haematuria and haemothorax have been reported in patients. Bleeding events of any grade, including purpura and petechiae, occurred in patients with haematological malignancies. Zanubrutinib may increase the risk of haemorrhage in patients receiving antiplatelet therapy or anticoagulant and patients should be monitored for signs of bleeding. Dose modification may be necessary for Grade 3 or greater adverse reactions as recommended. Warfarin or other vitamin K antagonists should not be administered concomitantly with zanubrutinib. Patients should be monitored for signs and symptoms of bleeding and full blood counts monitored. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with zanubrutinib.
- **Infections:** Serious infections (bacterial, viral or fungal) including fatal and non-fatal infections were observed in patients treated with zanubrutinib. Grade 3 or higher infections occurred in patients. Consider prophylaxis according to standard of care in patients who are at increased risk of infections. Patients should be monitored for signs and symptoms of infection and treated appropriately.
- **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.
- **Cytopenias:** Grade 3 or 4 cytopenias, including neutropenia, thrombocytopenia, and anaemia based on laboratory measurements, were reported in patients treated with zanubrutinib. Monitor full blood counts monthly for the first three months of treatment and then, three monthly.
- **Second primary malignancies**: Second primary malignancies, including non-skin carcinoma, have occurred in patients treated with zanubrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma). Monitor patients for the appearance of skin cancers and advise protection from sun exposure.
- **Atrial fibrillation and flutter**: Atrial fibrillation and atrial flutter have occurred in patients treated with zanubrutinib, particularly in patients with cardiac risk factors, hypertension and acute infections. Monitor for signs and symptoms of atrial fibrillation and atrial flutter and manage as appropriate.
- **Tumour lysis syndrome (TLS):** TLS has been infrequently reported with zanubrutinib therapy, particularly in patients who were treated for CLL. Assess relevant risks and take appropriate precautions. Monitor patients closely and treat as appropriate.

DRUG INTERACTIONS:

- Zanubrutinib is primarily metabolised by cytochrome P450 enzyme 3A (CYP3A). Concomitant use of zanubrutinib and medicinal products that strongly or moderately inhibit CYP3A can increase zanubrutinib exposure. Concomitant use of zanubrutinib and strong or moderate inducers of CYP3A can decrease zanubrutinib plasma concentrations. Please refer to Table 3 for dose modifications of zanubrutinib when co-administered with CYP3A inhibitors or inducers.
- Zanubrutinib is a mild inducer of CYP3A and CYP2C19. Concomitant use of zanubrutinib can decrease the plasma concentrations of these substrate medicinal products. Narrow therapeutic index medicinal products that are metabolised by CYP3A or CYP2C19 should be used with caution, as zanubrutinib may decrease the plasma exposures of these medicinal products.
- 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.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

- **For ordering information, please contact the company directly at the following email address:** ie.orders@beigene.com

REFERENCES:

1. Tam CS et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020 Oct 29; 136(18):2038-2050. doi: 10.1182/blood.2020006844. PMID: 32731259; PMCID: PMC7596850.
2. Tam CS et al. A head-to-head Phase III study comparing zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. Future Oncol. 2018 Sep; 14(22):2229-2237. doi: 10.2217/fon-2018-0163. Epub 2018 Jun 5. PMID: 29869556.
3. Tam CS et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol. 2022 Aug; 23(8):1031-1043. doi: 10.1016/S1470-2045(22)00293-5. Epub 2022 Jul 7. Erratum in: Lancet Oncol. 2023 Mar; 24(3):e106. PMID: 35810754.
4. Hillmen P et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. J Clin Oncol. 2023 Feb 10; 41(5):1035-1045. doi: 10.1200/JCO.22.00510. Epub 2022 Nov 17. PMID: 36395435; PMCID: PMC9928683.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
6. Zanubrutinib (Brukinsa®) Summary of Product Characteristics. Accessed July 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/brukinsa-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	25/03/2022		Dr Hilary O'Leary
2	12/09/2023	Regimen reviewed, new indication added (00708b and c). Baseline testing, adverse effects and supportive care sections updated.	Dr Hilary O'Leary

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.