Zanubrutinib (Brukinsa®) as monotherapy for the treatment of patients with waldenström's macroglobulinaemia (WM)

General information

Drug description [1]	Indication [2]
Zanubrutinib is a highly selective Bruton tyrosine kinase (BTK) inhibitor.	Zanubrutinib as monotherapy is indicated 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.

Current treatment [3]

- There is currently no cure for WM and treatments aim to control the disease and symptoms.
- Many people will be asymptomatic and will not require treatment for years (a few people will never require treatment). During this time, a 'watch and wait' strategy is employed with patients having regular (3-6 months) check-ups and blood tests (to measure IgM levels and blood cell counts).
- Treatment will start if troublesome symptoms start, blood IgM levels increase or blood cell counts change (development of anaemia, neutropenia or thrombocytopenia).
- There are several different types of treatment available for WM, including:
  - **Chemotherapy – first line**
    - Rituximab in combination with:
      - Dexamethasone and cyclophosphamide
      - Bendamustine
      - Fludarabine
      - Fludarabine and cyclophosphamide
      - Cladribine
    - Chemotherapy regimens without rituximab:
      - Cyclophosphamide, vincristine, doxorubicin and prednisolone
  - **Stem cell transplant**
    - Autologous
    - Allogenic
  - **Plasmapheresis**
  - **Other drugs**[1]
    - Bortezomib – proteasome inhibitor
    - Bendamustine – DNA synthesis inhibitor
    - Thalidomide – TNF Inhibitor
    - Ofatumumab – monoclonal antibody
    - Idelalisib – phosphoinositide 3-kinase inhibitor
    - Ibrutinib – BTK inhibitor (NICE technology appraisal currently in development for use in WM)
- Chemotherapy regimens are given over several months with one drug administered over several weeks followed by a break and another drug over the following weeks. The chemotherapy regime chosen will depend on individual factors such as general health, symptoms and potential future treatments required (e.g. stem cell transplant).

Regulatory status

EMA [2]	FDA [4, 5]
Approval status for this indication: On 16 September 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Brukinsa®, intended for the treatment of WM.	**Approval status for this indication**: On 31 August 2021, the FDA approved zanubrutinib (Brukinsa®) for adult patients with WM. **Other indications**: Brukinsa® is indicated for the treatment of adult patients with: ❖ Mantle cell lymphoma who have received at least one prior therapy (indication approved under accelerated approval based on overall response rate).

[1] Not licenced or not approved for use in WM by NICE in the UK.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 22/11/2021

The full indication is:

Brukinsa® as monotherapy is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy.

Other indications: none

✓ **Medicine is under additional monitoring**

- ❖ Relapsed or refractory marginal zone lymphoma who have received at least one anti-CD20-based regimen (indication approved under accelerated approval based on overall response rate).

✓ **Fast Track designation**
✓ **Orphan designation**

Costs

120 Brukinsa® hard capsules 80 mg = **€ 4,936.57** (ex-factory price) [6]

Warnings and precautions [4]

- ❖ **Haemorrhage:**
  - Monitor for bleeding and manage appropriately.
- ❖ **Infections:**
  - Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed.
- ❖ **Cytopenias:**
  - Monitor complete blood counts during treatment.
- ❖ **Second Primary Malignancies:**
  - Other malignancies have occurred in patients including skin cancers. Advise patients to use sun protection.
- ❖ **Cardiac Arrhythmias:**
  - Monitor for atrial fibrillation and atrial flutter and manage appropriately.
- ❖ **Embryo-Foetal Toxicity:**
  - Can cause foetal harm. Advise women of the potential risk to a foetus and to avoid pregnancy.

Study characteristics [1, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ASPEN BGB-3111-302 NCT03053440	201 (102 vs. 99)	zanubrutinib, 160mg twice daily, in 28-day cycles until progression or intolerance (cohort 1)	ibrutinib at a dose of 420 mg once daily	proportion of patients in cohort 1 who achieved a VGPR or CR (as assessed by an IRC)	randomised, open-label phase 3 trial	-	BeiGene Inc	[1]

Efficacy (I vs. C)

Primary analysis:

CR: No patient achieved a CR.

VGPRs (IRC-assessed): 28% vs. 19%, respectively, 2-sided p=0.09 (29% vs. 20%; p=0.12 among R/R patient and 26% vs. 17%; p=0.54 among TN patients)

VGPR (investigator-assessed): 28% and 17% (p=0.04)

Safety (I vs. C)

Grade ≥3 AEs: 58% vs. 63%

Grade ≥1 SAEs: 40% vs. 41%

Concordance rates between IRC- and investigator-assessed best responses: 94% vs. 95% **MRRs**: 77% vs. 78% overall (78% vs. 80% among R/R patients, and 74% vs. 67% among TN patients) **Median times to achieve a VGPR**: 5.6 vs. 22.1 months (p=0.35) among TN patients; 4.7 vs. 5.1 months (p=0.17) among R/R patients **Median time to major response**: 2.8 months (for both arms) **Median DOR**: NR **18-month event-free rates for major responders**: 85% vs. 88% overall, 87% vs. 86% for R/R patients **After median follow-up for PFS of 18.0 and 18.5 months**: 15% and 16% of patients progressed or died **Median PFS**: NR **Event-free rates at 18 months**: 85% vs. 84% overall; 86% vs. 82% for R/R patients **Deaths**: n=6 (n=3 R/R; n=3 TN) and n=8 (n=8 R/R; n=0 TN) **Estimated OS rates at 18 months**: 97% vs. 93% **Median IgM levels**: reduced by 79% vs. 72% **Median baseline hemoglobin concentrations**: 103 g/L vs.109 g/L **Median maximal hemoglobin concentrations** increased by 27 g/L vs. 28 g/L **Reductions in bone marrow infiltration**: 69% vs. 73%; median maximal reductions from baseline were 10% vs. 15% **Reductions in lymph node and/or spleen dimensions**: 81% vs. 80% Based on an **updated data cut-off** the PFS event-free rate (by investigator assessment) was 84.9% vs. 77.6% at 30 months, with an estimated overall HR of 0.734 (95% CI: 0.380-1.415) [9]. **QoL**: ❖ In most QoL assessments, zanubrutinib trended toward greater improvement, particularly among patients who achieved a VGPR. ❖ This was most notable in the European Quality of Life Five Dimensions Questionnaire and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 subscales of appetite, dyspnea, fatigue, physical functioning, and role functioning. ❖ The symptom subscale for diarrhoea trended worse for ibrutinib patients than for zanubrutinib patients, consistent with the frequency of diarrhoea reported for each treatment arm.	**Deaths attributed to AEs:** n=3 (all R/R patients)[2] **Discontinuation[3]:** 4% vs. 9%

Risk of bias (RCT) [10]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	no	no, open-label	unclear[4]	yes[5]	high
					First published: 10/2021 **Last updated**: 01/2022

Abbreviations: AE=adverse event, BTK=Bruton tyrosine kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DOR=duration of response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, IgM=immunoglobulin M, IRC= independent review committee,

[2] 2 deaths in ibrutinib patients resulted from complications of sepsis, and 1 zanubrutinib patient died from complications of cardiac arrest postplasmapheresis.
[3] Discontinuation due to AE(s)
[4] The ASPEN trial is currently ongoing; estimated study completion date is 01/2022.
[5] This study was supported by research funding from the sponsor.

MRR=major response rate, n=number of patients, NR=not reached, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life, R/R=relapsed/refractory, SAE=serious adverse event, TN=treatment-naïve, VGPR=very good partial response, WM=Waldenström's macroglobulinaemia

References:

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