Zanubrutinib Fact Sheet

(ZAN-ue-BROO-tih-nib)

Generic Name: Zanubrutinib
Trade Name: Brukinsa® from BeiGene
Other Names: BGB-3111

Drug Type: Zanubrutinib is a targeted therapy. Targeted therapy is the result of years of research dedicated to understanding the differences between cancer cells and normal cells. This information is used to create a therapy to attack the cancer cells while causing minimal damage to the normal cells, leading to fewer side effects. Each type of targeted therapy works a little differently, but all interfere with the ability of the cancer cell to grow, divide, repair and/or communicate with other cells.

Zanubrutinib, like ibrutinib – currently the only US Food and Drug Administration (FDA) approved treatment of Waldenstrom's macroglobulinemia [WM]) and acalabrutinib – inhibits the function of Bruton's tyrosine kinase (BTK). BTK is a key signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival of malignant B-cells. Zanubrutinib blocks signals that stimulate malignant B-cells to grow and divide uncontrollably.

What Conditions Are Treated by Zanubrutinib:
Zanubrutinib is currently approved by the FDA for the treatment of mantle cell lymphoma (MCL) in patients who have received at least one prior therapy.

Without specific FDA approval for treating WM, when zanubrutinib is prescribed for patients with WM it is given "off-label", signifying the drug is being prescribed for an unapproved indication or in an unapproved age group, dosage, or route of administration. This ability to prescribe drugs for uses beyond officially approved indications is common in medicine and includes most other drugs used to treat WM, except for ibrutinib and the combination of ibrutinib with rituximab.

The period after treatment when a WM patient has experienced either stabilization of disease, an improvement in disease status, or even, unfortunately, disease progression is called a "response". While an improvement in disease status is sometimes commonly referred to as a "remission", the preferred scientific terminology is "response". Response to treatment and duration of response vary widely in WM. Currently, there is no way to accurately predict how good or how long a response will be for an individual patient. One of the goals of WM researchers is to better determine how patients will respond to a particular treatment based on the variations in each person's disease biology and unique genetic makeup.

In a Phase I study of patients with WM, zanubrutinib induced an overall response rate (ORR) of 92% and very good partial response (VGPR) of 43%, with a favorable safety and tolerability profile. A large head-to-head, multicenter Phase III trial in 229 patients with relapsed/refractory (R/R) or treatment naive WM conducted in 61 centers in Australia, Europe, and the United States, compared zanubrutinib to ibrutinib as a monotherapy. While the trial did not achieve statistical significance of superiority in the overall response rate (ORR), major response rate (MR), and very good partial response rate (VGPR) of zanubrutinib compared to ibrutinib, zanubrutinib did demonstrate a higher VGPR rate compared to ibrutinib (28.4% vs. 19.2%) as well as consistent improvements in safety and tolerability in this first

randomized comparative trial within the BTK inhibitor class. These Phase III results have not been peer -reviewed nor published, as of the date of this publication. Further testing will be needed to confirm if this is true, as well as whether outcomes for patients with WM can be improved with zanubrutinib combination therapies. Additionally, there is a case report of a patient with Bing-Neel syndrome who was effectively treated with zanubrutinib.

Table 1. Phase I Clinical Trial with Zanubrutinib Monotherapy

Response Criteria for WM (Modified from 6th International Workshop on WM)	Zanubrutinib Median Follow-up 24 Months
Overall Response Rate (ORR) –At least a minor response (CR+VGPR+PR+MR)	92%
Major Response (MR) Rate –At least a partial response (CR+VGPR+PR)	82%
Very Good Partial Response Rate (VGPR) – ≥90% reduction of M-protein, resolution of adenopathy/organomegaly, and no new signs or symptoms of active disease	43%
Partial Response (PR) Rate – ≥50% reduction of M-protein, resolution of adenopathy/organomegaly, and no new signs or symptoms of active disease	37%
Minor Response Rate –25%-49% reduction of IgM, no new signs or symptoms of active disease	12%

Table 2. Phase III Head to Head Clinical Trial of Zanubrutinib versus Ibrutinib (Unpublished results)

Response Criteria for WM (Modified from 6th International Workshop on WM)	Zanubrutinib Median Follow-up 19.4 Months	Ibrutinib Median Follow-up 19.4 Months
Overall Response Rate (ORR) –At least a minor response (CR+VGPR+PR+MR)	97%	93%
Major Response (MR) Rate –At least a partial response (CR+VGPR+PR)	77.5%	77.8%
Very Good Partial Response Rate (VGPR) – ≥90% reduction of M-protein, resolution of adenopathy/organomegaly, and no new signs or symptoms of active disease	28.4%	19.2%

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How Zanubrutinib Is Given:
The dose of zanubrutinib will be different for different patients. Follow the instructions from your healthcare team or the directions on the label. The following information includes only the average doses of zanubrutinib. If your dose is different, do not change it unless the healthcare team tells you to do so.

In the United States, zanubrutinib is available through specialty pharmacies. The usual dosage for WM is two 80 mg (160 mg) capsules, taken by mouth twice daily, approximately 12 hours apart at the same times each day, continued until disease progression or unacceptable tolerability is demonstrated. The capsule should be swallowed whole (not crushed, opened, chewed, or dissolved) with at least 8 ounces of water. The drug may be taken with food or on an empty stomach. Zanubrutinib should be taken exactly as prescribed. If a dose is missed, it should be taken as soon as remembered on the same day with a return to the normal schedule the following day. The dose should not be changed, nor the drug stopped, unless instructed to do so by a healthcare provider. Store zanubrutinib capsules at room temperature, between 68 to 77 degrees F (20 to 25 degrees C).

The recommended dose of zanubrutinib may be decreased in patients with severe liver impairment. The dose of zanubrutinib may also be modified due to drug interactions, such as many antiseizure, antifungal, and antibacterial medications. Taking zanubrutinib with any of the following drugs is usually not recommended but may be required in some cases. If both medicines are prescribed together, the healthcare team may change the dose or how often one or both medicines are used. The following list may not be all-inclusive:

Apalutamide
Aprepitant
Atazanavir
Boceprevir
Bosentan
Carbamazepine
Ciprofloxacin
Clarithromycin
Cobicistat
Conivaptan
Crizotinib
Cyclosporine
Diltiazem
Dronedarone
Efavirenz
Enzalutamide
Erythromycin
Etravirine
Fluconazole
Fluvoxamine
Fosnetupitant
Fosphenytoin
Idelalisib
Imatinib
Indinavir
Itraconazole
Ketoconazole
Letermovir
Lopinavir
Lorlatinib
Lumacaftor
Mitotane
Modafinil
Nafcillin
Nefazodone
Nelfinavir
Netupitant
Nilotinib
Phenobarbital
Phenytoin
Posaconazole
Primidone
Rifabutin
Rifampin
Ritonavir
Saquinavir
St John's Wort
Telaprevir
Telithromycin
Verapamil
Voriconazole

Do not take other medicines unless they have been discussed with the healthcare team. This includes prescription or nonprescription (over-the-counter [OTC]) medicines and herbal or vitamin supplements. Grapefruit and grapefruit juice should also not be consumed during treatment with zanubrutinib.

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Side Effects Associated with Zanubrutinib:
Although the Phase III trial demonstrated consistent improvements in safety and tolerability for zanubrutinib in patients with WM, zanubrutinib may infrequently cause serious, life-threatening side effects, including severe bleeding problems (hemorrhage), infections, decreased blood cell counts, new cancers, such as skin cancer, and heart rhythm problems.

The most common side effects for patients taking zanubrutinib are neutropenia (low numbers of circulating neutrophils, a type of white blood cell), thrombocytopenia (low number of platelets necessary for clotting of the blood), upper respiratory tract infection (e.g., the common cold), low numbers of total white blood cells, anemia (low numbers of circulating red blood cells), rash, diarrhea, bruising, and cough. Less common side effects include muscle pain, pneumonia, urinary tract infection, hematuria (blood in the urine), fatigue, constipation, and bleeding events that are more than bruising, such as hemorrhage.

Another potentially serious side effect of zanubrutinib is atrial fibrillation and atrial flutter. The risk may be increased in patients with cardiac risk factors; hypertension (high blood pressure), prior arrhythmias (heart beats with irregular or abnormal rhythm), and acute infection. Patients on zanubrutinib should be regularly monitored for symptoms of arrhythmias (palpitations, dizziness, dyspnea (shortness of breath), as well as serious infections, bleeding/hemorrhage, and low blood counts, and should be treated appropriately.

Zanubrutinib can make skin more sensitive to sunlight and may raise the chance of skin cancer; consequently, time in the sun should be limited, sunscreen should be used, and hats and clothes worn to cover as much skin as possible.

Side effects that are very rare, occurring in fewer than 10% of patients are not listed here. There is no relationship between the presence and/or severity of side effects and the effectiveness of the medication. The side effects associated with zanubrutinib may be quite manageable; however, side effects should always be reported to a healthcare provider. Most people will not experience all the side effects listed. Side effects are often predictable in terms of their onset, duration, and severity. They are almost always reversible and will go away after therapy is completed.

Males and females of reproductive age should use effective contraception during treatment and for at least one week after the last dose of the drug (if told to stop treatment due to disease progression or unmanageable side effects). Women who are pregnant or breastfeeding should not take the drug, as zanubrutinib may cause fetal harm and it is unknown if the drug is present in breast milk.

When to Contact Your Doctor or Health Care Provider:
Contact your doctor or healthcare provider immediately, day or night, if you should experience any of the following symptoms: fever of 100.4° F (38° C) or higher or chills (both are possible signs of infection), shortness of breath or trouble breathing, cough, or any bleeding that won't stop.

Inform the healthcare team of any signs or symptoms of bleeding, including bloody stools or black, tar-like stools, pink or brown urine, unexpected or severe bleeding, vomit with blood in it or vomit that looks like coffee grounds, coughing up blood or blood clots, increased bruising, dizziness, weakness, confusion, changes in speech, or headaches that last a long time. Decreased blood counts (white blood

cells, platelets, and red blood cells) are common with zanubrutinib, but they can also be severe. The healthcare team should do blood tests during treatment with zanubrutinib to check for changes in blood counts. Always inform your health care provider if you experience any unusual symptoms.

Self-Care Tips While Taking Zanubrutinib:
Patients should avoid consumption of grapefruit, grapefruit juice, and herbal supplements, such as St. John's Wort, during treatment with zanubrutinib. Zanubrutinib may further increase the risk of bleeding in patients taking blood thinner medicines, including aspirin. Any planned surgeries or dental procedures should be discussed with a healthcare provider. Depending on the bleeding risk, zanubrutinib may need to be discontinued for a short period of time (3-7 days) before and after the procedure.

Zanubrutinib may reduce the efficacy of inactivated (not live) vaccines. Immunizations or vaccinations should not be administered without a healthcare provider's approval while taking zanubrutinib. Complete all appropriate vaccines at least two weeks before starting the drug. If vaccinated during therapy, revaccinate at least three months after discontinuing zanubrutinib. Avoid use of live organism vaccines with immunosuppressant therapies, such as zanubrutinib. Before starting zanubrutinib inform your healthcare provider if you have or had hepatitis B virus (HBV) infection, as serious infections can occur during treatment.

Stay well hydrated and drink at least 2-3 quarts of fluid every 24 hours, unless you are instructed otherwise.

Wash your hands often with soap and water and try to keep your hands away from your nose and mouth.

There is an increased risk of infection so try to avoid crowds or people with colds and report fever or any other signs of infection immediately to your healthcare provider.

Make sure you tell your doctor and pharmacist about any other medications you are taking (including prescription, over-the-counter, vitamins, herbal remedies, etc.), with emphasis on anticoagulants and other medications that affect platelet aggregation.

Use an electric razor and a soft toothbrush to minimize bleeding.

Avoid contact sports or activities that could cause injury.

If you have nausea, ask your healthcare provider about prescription anti-nausea medication and eat small, frequent meals to minimize nausea. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely while taking zanubrutinib. Alcohol consumption during treatment should always be discussed with a healthcare provider.

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Eat foods that may help reduce diarrhea:

- Drink plenty of clear fluids (8-10 glasses per day). Examples: Gatorade®, broth, Jello®, water, etc.
- Eat small amounts of soft bland low fiber foods frequently. Examples: banana, rice, noodles, white bread, skinned chicken, turkey, or mild white fish.
- Avoid foods such as:
    - Greasy, fatty, or fried foods.
    - Raw vegetables or fruits.
    - Strong spices.
    - Whole grain breads and cereals, nuts, and popcorn.
    - Gas forming foods and beverages (beans, cabbage, carbonated beverages).
    - Lactose-containing products, supplements, or alcohol.
    - Limit foods and beverages with caffeine and beverages extremely hot or cold.

If you have diarrhea, your doctor can prescribe and/or recommend over-the-counter anti-diarrhea medications, such as loperamide.

Avoid sun exposure. Wear SPF 30 (or higher) sun block and protective clothing.

While it is always important to get plenty of rest and maintain good nutrition, this is even more important while being treated with any targeted therapy, including zanubrutinib.

Tell all your healthcare providers that you take zanubrutinib. This includes your doctors, nurses, pharmacists, and dentists. If side effects or symptoms are experienced while being treated with zanubrutinib, tell your healthcare provider. They can prescribe medications and/or offer suggestions that are effective in managing these problems.

This document does not contain all possible drug interactions.

Monitoring and Testing While Taking Zanubrutinib:
You will be checked regularly by your doctor while you are taking zanubrutinib to monitor side effects and check your response to therapy. Periodic blood work will be obtained to monitor your complete blood count (CBC) as well as the function of other organs (such as your kidneys and liver).

NOTE: The information in this fact sheet is intended to be helpful and educational, but it does not constitute an endorsement by the IWMF and is not meant to be a substitute for professional medical advice. The IWMF strongly encourages discussions with healthcare professionals about specific medical conditions, side effects, and treatments.

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Adapted from the BeiGene website, www.brukinsa.com, Lexicomp© website www.wolterskluwercdi.com/lexicomp-online and Mayo Clinic website www.mayoclinic.org/drugs-supplements/zanubrutinib-oral-route/before-using/drg-20477009