PDL DRUG REVIEW

Proprietary Name: Brukinsa®
Common Name: zanubrutinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Calquence	Non-Recommended with Conditions
Imbruvica	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Zanubrutinib, the active ingredient of Brukinsa®, is a Bruton's tyrosine kinase (BTK) inhibitor. It is a small-molecule inhibitor of BTK that forms a covalent bond with a cysteine residue in the BTK active site**,** leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In non-clinical studies, zanubrutinib inhibited malignant B-cell proliferation and reduced tumor growth.

Indications: For the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

There is no pregnancy category for this product; however, the risk summary indicates that based on findings in animals, use can cause fetal harm when given to a pregnant woman. There are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Women should be advised to avoid pregnancy while taking Brukinsa®. If Brukinsa® is used during pregnancy or the patient becomes pregnant while taking the treatment, the patient should be apprised of the potential hazard to the fetus. Pregnancy testing is recommended for females of reproductive potential prior to starting Brukinsa® therapy and this population should use effective contraception during treatment and for at least 1 week after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Capsules, 80mg. Do not open, break, or chew the capsules.

Recommended Dosage: Take 160mg PO BID or 320mg PO QD until disease progression or unacceptable toxicity. Take with or without food but advise patients to swallow capsules whole with water.

There are recommended dose modifications of Brukinsa® for grade 3 or higher adverse reactions, such as non-hematological toxicities, febrile neutropenia, thrombocytopenia with significant bleeding, neutropenia, or thrombocytopenia. Please refer to the prescribing information for additional information.

Monitor for adverse reactions in patients with hepatic impairment. Dose modifications are not recommended in patients with mild to moderate hepatic impairment but reduce to 80mg PO BID with severe hepatic impairment. Dose adjustments are not required with mild to moderate renal impairment. Monitor for adverse reactions in patients with severe renal impairment.

Drug Interactions: The co-administration of Brukinsa® with a moderate or strong CYP3A inhibitor increases zanubrutinib Cmax and AUC. Reduce Brukinsa® dosage when co-administered with moderate or strong CYP3A inhibitors. With a strong CYP3A inhibitor, reduce the Brukinsa® dose to 80mg PO QD. With a moderate CYP3A inhibitor, reduce the Brukinsa® dose to 80mg PO BID. The co-administration of Brukinsa® with a moderate or strong CYP3A inducer decreases zanubrutinib Cmax and AUC. Avoid the co-administration of Brukinsa® with moderate or strong CYP3A inducers.

Box Warning: There is no box warning with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Brukinsa®) for all grades. There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included neutropenia and neutrophil count decreased (38%), thrombocytopenia and platelet count decreased (27%), leukopenia and white blood count decreased (25%), anemia and hemoglobin decreased (14%), upper respiratory tract infection (39%), pneumonia (15%), urinary tract infection (11%), rash (36%), bruising (14%), diarrhea (23%), constipation (13%), hypertension (12%), hemorrhage (11%), musculoskeletal pain (14%), hypokalemia (14%), and cough (12%). Selected laboratory abnormalities include neutrophils decreased (45%), platelets decreased (40%), hemoglobin decreased (27%), lymphocytosis (41%), blood uric acid increased (29%), ALT increased (28%), and bilirubin increased (24%).

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with Brukinsa® monotherapy. Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of Brukinsa® with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding. Discontinue treatment if intracranial hemorrhage of any grade occurs.

Fatal and serious infections and opportunistic infections have occurred in patients with hematological malignancies treated with Brukinsa®. The most common Grade 3 or higher infection was pneumonia. Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia, and other infections per standard of care in patients who are at increased risk for infections. Monitor and assess patients for fever or other signs/symptoms of infection.

Due to reports of cytopenias in patients treated with Brukinsa®, monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with Brukinsa® monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with Brukinsa® monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Beigene USA, Inc

Analysis: The safety and efficacy of Brukinsa® were assessed in a Phase 2, open-label, multicenter, single-arm trial (Study 1) of previously treated patients with MCL (N=86) who had received at least one prior therapy. The median age of included adults was 60.5 years (range 34 to 75 years) and most were male (78%). The median

time since diagnosis to study entry was 30 months, and the median number of prior therapies was 2 (range 1 to 4). The most common prior regimens were CHOP-based (91%) followed by rituximab-based (74%).

The efficacy of Brukinsa® was also assessed in a second study, a Phase 1/2 open-label, dose escalation, multicenter, single-arm trial of B-cell malignancies that included previously treated MCL patients (N=32) treated with Brukinsa® (Study 2). The median age of patients was 70 years (range 42 to 86) and 38% of the patients were ≥75 years of age. Most patients were male (69%) and Caucasian (78%).

Tumor response was per the 2014 Lugano Classification for both studies, and the primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee. Results can be seen in the table below, which was adapted from the prescribing information.

	Study 1 (N=86)	Study 2 (N=32)
ORR	84%	84%
Complete Response	59%	22%
Partial Response	24%	62%
Median Duration of Response, months	19.5	18.5

Place in Therapy: Brukinsa® is an oral Bruton's tyrosine kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The efficacy of Brukinsa® was seen in two open-label, single-arm studies, with overall response rate being 84% in both studies.

It is recommended that Brukinsa® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Brukinsa [package insert]. San Mateo, CA: BeiGene USA, Inc; 2019.