INDICATIONS
BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with:
• Waldenström’s macroglobulinemia (WM).
• Mantle cell lymphoma (MCL) who have received at least one prior therapy.
• Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

The MCL and MZL indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients 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 BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
BRUKINSA Dosing Flexibility

2 Dosing Options

Recommended dose is 320 mg daily.

- Two 80-mg capsules **TWICE DAILY**
  - am 160 mg
  - pm 160 mg
  - OR
  - 320 mg

- Four 80-mg capsules **ONCE DAILY**

Can be coadministered with gastric acid reducing agents (including PPIs, H2RAs, and antacids)

- 20% to 55% of cancer patients receive gastric acid reducing agents

Administration

- Can be taken with or without food. Can be taken with a high-fat meal—BRUKINSA drug concentration (AUC) is not affected
- Advise patients to swallow capsules whole with water—do not open, break, or chew capsules
- If a dose of BRUKINSA is missed, it should be taken as soon as possible with a return to the normal schedule the following day

BRUKINSA should be taken until disease progression or unacceptable toxicity.

How Supplied and Storage

<table>
<thead>
<tr>
<th>Strength</th>
<th>Package Size</th>
<th>NDC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg</td>
<td>120 capsules</td>
<td>72579-011-02</td>
</tr>
</tbody>
</table>

- Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F)

Recommended Dose Adjustments

CYP3A Inhibitors or Inducers

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate CYP3A inhibitors (such as erythromycin, fluconazole, and verapamil)</td>
<td>80 mg twice daily</td>
</tr>
<tr>
<td>Strong CYP3A inhibitors (such as clarithromycin and itraconazole)</td>
<td>80 mg once daily</td>
</tr>
<tr>
<td>Moderate CYP3A inducers (such as bosentan, efavirenz, and phenobarbital)</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Strong CYP3A inducers (such as carbamazepine, phenytoin, and rifampin)</td>
<td>Avoid concomitant use</td>
</tr>
</tbody>
</table>

After discontinuation of a CYP3A inhibitor, resume previous dose of BRUKINSA.

Hepatic Impairment

<table>
<thead>
<tr>
<th>Level of Impairment*</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Severe</td>
<td>80 mg twice daily</td>
</tr>
</tbody>
</table>

*Based on Child-Pugh score. AUC=area under the concentration-time curve; H2RAs=H2-receptor antagonists; PPIs=proton pump inhibitors.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection, and monitor patients for the development of second primary malignancies.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
No Dose Adjustments With These Common Medications

Gastric Acid Reducing Agents
Proton pump inhibitors
Including, but not limited to:
• Omeprazole
• Esomeprazole
• Lansoprazole
H2-receptor antagonists
Including, but not limited to:
• Famotidine
• Ranitidine
• Nizatidine

Anticlotting Medications
Anticoagulants
Including, but not limited to:
• Heparins
• Direct thrombin inhibitors
• Factor Xa inhibitors
• Vitamin K antagonists
Antiplatelets
Including, but not limited to:
• Aspirin
• P2Y12 inhibitors
• Phosphodiesterase inhibitors
• PAR-1 antagonists

BRUKINSA was allowed to be coadministered in clinical trials with antiplatelets and anticoagulants (as long as INR was ≤1.5 and aPTT ≤1.5 x ULN).\(^5\,^7\)

Coadministration of BRUKINSA with antiplatelet or anticoagulation medications may increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding.\(^1\)

Renal Impairment
No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥15 mL/min).

Hepatic Impairment
No dosage modification is recommended in patients with mild to moderate hepatic impairment.

Cardiac Arrhythmias
Monitor for signs and symptoms of atrial fibrillation or atrial flutter and manage as appropriate.

Hepatitis B and Hepatitis C
Patients with serologic evidence of active hepatitis B (HBV) or hepatitis C (HCV) were excluded from study.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (continued)

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity
Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for 1 week after the last dose. Advise men to avoid fathering a child during treatment and for 1 week after the last dose.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
**Demonstrated Safety Profile in Clinical Trials**

**Combined ARs in ≥10% of Patients With Hematologic Malignancies (N=847)\(^8\)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
<td>0.7</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Bruising</td>
<td>25</td>
<td>0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>23</td>
<td>0.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>Herpesvirus infection</td>
<td>10</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Chronic lymphocytic leukemia, Waldenström’s macroglobulinemia, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia, diffuse large B-cell lymphoma, and Richter’s transformation.*

**ARs of Special Interest in Patients With Hematologic Malignancies (N=847)\(^8\)**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades (%)</th>
<th>Grades &gt;3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>Atrial fibrillation or atrial flutter</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Dose Modifications for ≥Grade 3 Adverse Reactions**

**ARs That Require Dose Modifications\(^1\)**
- Grade 3 or higher non-hematological 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)

**Recommended Dose Modifications by Occurrence for ≥Grade 3 ARs\(^1\)**

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>1st Occurrence</th>
<th>2nd Occurrence</th>
<th>3rd Occurrence</th>
<th>4th Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No dose change</td>
<td>Reduce to 160 mg Total Dose</td>
<td>Reduce to 80 mg Total Dose</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Start at 320 mg Total Dose (160 mg twice daily or 320 mg once daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice-daily Dosing</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
<tr>
<td>Once-daily Dosing</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
<td>AM PM</td>
</tr>
</tbody>
</table>

**No dose exchange required for dose modification**

- Low rates of dose reductions (0.8%-11%) or treatment discontinuation (2%-7%) across BRUKINS SA studies\(^1\)

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (continued)**

**Cytopenias**
Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINS SA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients.
Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
Flexible Dosing to Meet Patient Needs

Two flexible dosing options

BRUKINSA can be taken as 160 mg twice daily or 320 mg once daily

No dose adjustments needed with common medications

Gastric acid reducing agents | Anticlotting medications

No dose exchange required for dose modifications

Dose modification for ≥ Grade 3 adverse reactions only requires reduction in number of capsules taken daily

myBeiGene® Patient Support
Dedicated Oncology Nurse Advocates provide personalized support for each patient’s needs

The myBeiGene patient support program can provide your office with reimbursement and payment assistance to help your patients gain access to BRUKINSA.

To enroll in myBeiGene, please visit BRUKINSA.com or call 1-833-234-4363.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N=847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) and musculoskeletal pain (30%).

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.

*BRUKINSA was allowed to be coadministered in clinical trials with antiplatelets and anticoagulants (as long as INR was ≤ 1.5 and aPTT ≤ 1.5 x ULN).5-7

aPTT=activated partial thromboplastin time; INR=International Normalized Ratio; ULN=upper limit of normal.