THE COMPLETE DOSING AND ADMINISTRATION GUIDE

INDICATIONS
BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:
• Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
• 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 hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemotherax have been reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration 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: Unmatched BTKi
dosing flexibility1-4

The Recommended Daily Dose of BRUKINSA Is 320 mg1

The only BTKi with dosing options1

Flexibility to tailor the schedule to your patients

ONCE DAILY
Consider for patients with compliance concerns or for those who prefer taking their medication once a day

320 mg daily dose
(four 80-mg capsules once daily)

TWICE DAILY
Consider for patients who take other twice-daily medications to maintain a consistent drug dosing schedule

320 mg daily dose
(two 80-mg capsules AM) + (two 80-mg capsules PM)

Administration1

- 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 Storage1

<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)

Hepatic Impairment1

<table>
<thead>
<tr>
<th>Level of Hepatic 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>

The only BTKi with recommended dosage for severe hepatic impairment†1,4

CYP3A Inhibitors or Inducers1,5

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A inhibitors (such as clarithromycin and itraconazole)</td>
<td>80 mg once daily Interrupt dose as recommended for adverse reactions.</td>
</tr>
<tr>
<td>Moderate CYP3A inhibitors (such as erythromycin, fluconazole, and verapamil)</td>
<td>80 mg twice daily Modify dose as recommended for adverse reactions.</td>
</tr>
<tr>
<td>Strong CYP3A inducers (such as carbamazepine, phenytoin, and rifampin)</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Moderate CYP3A inducers (such as bosentan, efavirenz, and phenobarbital)</td>
<td>Avoid concomitant use if these inducers cannot be avoided, increase BRUKINSA dose to 320 mg twice daily.</td>
</tr>
</tbody>
</table>

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

*Based on Child-Pugh score.
†Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.
AUC=area under the concentration-time curve; BTKi=Bruton’s tyrosine kinase inhibitor.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

Anticlotting Medications\textsuperscript{1,6}

\textbf{Anticoagulants} Including, but not limited to:
- Heparins
- Direct thrombin inhibitors
- Factor Xa inhibitors
- Vitamin K antagonists

\textbf{Factor Xa inhibitors}
- Rivaroxaban
- Apixaban
- Edoxaban

\textbf{Direct thrombin inhibitors}
- Dabigatran
- Argatroban

\textbf{Heparins}
- Low molecular weight heparin
- Unfractionated heparin

\textbf{Vitamin K antagonists}
- Warfarin
- Rivaroxaban
- Apixaban

\textbf{Phosphodiesterase inhibitors}
- Eprosartan

\textbf{PAR-1 antagonists}
- Prasugrel

\textbf{Aspirin}
- Aspirin

\textbf{Heparins}
- Ticagrelor

\textbf{Hydroxyurea}
- Hydroxyurea

\textbf{P2Y12 inhibitors}
- Clopidogrel

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).\textsuperscript{6-8} Coadministration of BRUKINSA with antiplatelet or anticoagulation medications may increase the risk of hemorrhage. Monitor for signs and symptoms of bleeding.\textsuperscript{1}

Gastric Acid Reducing Agents\textsuperscript{1}

\textbf{Proton pump inhibitors}
- Omeprazole
- Esomeprazole
- Lansoprazole

\textbf{H2-receptor antagonists}
- Famotidine
- Ranitidine
- Nizatidine

\textbf{PPIs (with caution)}
- Nizatidine
- Ranitidine

\textbf{Aspirin}
- Aspirin

\textbf{Famotidine}
- Famotidine

\textbf{Esomeprazole}
- Esomeprazole

\textbf{Lansoprazole}
- Lansoprazole

\textbf{Ampicillin}
- Ampicillin

No Dose Adjustments Needed in Select Populations

\textbf{Renal Impairment}\textsuperscript{1}
No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment (CrCl ≥15 mL/min).
Monitor for adverse reactions (ARs) in patients on dialysis.

\textbf{Hepatic Impairment}\textsuperscript{1}
No dose adjustment is recommended in patients with mild to moderate hepatic impairment.

Recommended dose adjustment in patients with severe hepatic impairment is 80 mg twice daily. Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.

Monitor for ARs in patients with hepatic impairment.

\textbf{Cardiac Arrhythmias}\textsuperscript{1}
Monitor for signs and symptoms of cardiac arrhythmias, manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

\textbf{Hepatitis B (HBV) and Hepatitis C (HCV)}\textsuperscript{1,7}
Patients with serologic evidence of active HBV or HCV were excluded from BRUKINSA clinical studies.

Infections due to hepatitis reactivation have occurred. If reactivation occurs, interrupt treatment with BRUKINSA.

\textbf{IMPORTANT SAFETY INFORMATION (continued)}

\textbf{WARNINGS AND PRECAUTIONS (continued)}

\textbf{Hepatitis B (HBV) and Hepatitis C (HCV)}\textsuperscript{1,7}

\textbf{Guidance on use of hepatitis reactivation prophylaxis}
- For patients with anti-HBc or anti-HCV, prophylaxis with nucleoside reverse transcriptase inhibitors should be considered.
- For patients with HBV reactivation, prophylaxis with anti-HBV therapy should be considered.

\textbf{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.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

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

**AEs in >10% of Patients With Hematologic Malignancies (N=1550)**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Grades (%)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>0.9</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Bruising</td>
<td>23</td>
<td>0.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>0.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>0.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0.3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Includes 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.1

AE-adverse event.

**AEs of Special Interest in Patients With Hematologic Malignancies (N=1550)**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>0.7</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Atrial fibrillation or atrial flutter</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Dose Modifications for ≥Grade 3 Adverse Reactions

**ARs That Require Dose Modifications**

- Grade 3 or Grade 4 febrile neutropenia
- Platelet count decreased to 25,000-50,000/mm³ with significant bleeding
- Neutrophil count decreased to <500/mm³
- Platelet count decreased to <25,000/mm³
- Severe or life-threatening non-hematological toxicities

**Recommended Dose Modifications by Occurrence for ≥Grade 3 ARs**

<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>Start at 320 mg Total Dose (160 mg twice daily or 320 mg once daily)</td>
<td>No change†</td>
<td>Reduce to 160 mg Total Dose</td>
<td>Reduce to 80 mg Total Dose</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Resume treatment once toxicity has resolved to ≤Grade 1 or baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Lasting more than 10 consecutive days.1

*Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.1

*The recommended daily dose of BRUKINSA is 320 mg.

Asymptomatic lymphocytosis should not be regarded as an adverse reaction, and these patients should continue taking BRUKINSA.1

<table>
<thead>
<tr>
<th>Low rates of dose reductions or treatment discontinuation across BRUKINSA studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose reductions: 0.8%-11%</td>
</tr>
<tr>
<td>• Treatment discontinuations: 2%-13%</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS**

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
Evaluate the benefit-risk before resuming treatment at the same dosage for Grade 4 non-hematological toxicity.

The recommended daily dose of BRUKINSA is 320 mg.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in 30% of patients were:

- Neutrophil count decreased
- Platelet count decreased
- Hemorrhage
- Musculoskeletal pain
- Gastrointestinal perforation

Recommended Dose Modifications by Occurrence

- Platelet count decreased to <25,000/mm³
- Neutrophil count decreased to <500/mm³

ARs That Require Dose Modifications

- Platelet count decreased to <25,000/mm³
- Neutrophil count decreased to <500/mm³

No dose exchange required for dose modification.

Flexible Dosing to Meet Patient Needs

- BRUKINSA can be taken as 160 mg twice daily or 320 mg once daily.
- The only BTKi with recommended dosage for severe hepatic impairment:
  Adjust dose to 80 mg twice daily. No dose adjustment needed for mild to moderate hepatic impairment.
- Straightforward dose modifications without exchanges:
  Dose modification for ≥Grade 3 adverse reactions only requires reduction in number of capsules taken daily.

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

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

*Although the safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment, there is no caution to avoid use in these patients.*

**References:**

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