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 hemothorax 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. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

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.

NEW LONG-TERM DATA:
~4 YEAR DATA vs BR IN 1L
~3 YEAR DATA vs IBRUTINIB IN 2L

1L=first line; 2L=second line; BR=bendamustine+rituximab; CLL=chronic lymphocytic leukemia.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMPORTANT SAFETY INFORMATION

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Please see additional Important Safety Information throughout, and accompanying full Prescribing Information.
BRUKINSA DELIVERS POWERFUL EFFICACY IN PATIENTS WITHOUT AND WITH DEL(17p)\(^3,4\)

Initial Analysis (26 months in Cohort 1, 31 months in Cohort 2)

Superior PFS vs BR: patients without del(17p)\(^3,4\)

(Cohort 1: primary endpoint)

Consistent PFS in BRUKINSA-only arm: patients with del(17p)\(^3,4\)

<table>
<thead>
<tr>
<th>Month</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
<th>BRUKINSA</th>
</tr>
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<tbody>
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<td>100</td>
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<td>...</td>
</tr>
</tbody>
</table>

Median PFS was not reached in either arm.\(^3,4\)

Prespecified analysis assessed by IRC.\(^4\)

SEQUOIA was a global Phase 3, randomized, open-label, multicenter trial evaluating BRUKINSA vs BR in 479 patients with previously untreated CLL/SLL without del(17p). 110 patients with del(17p) were evaluated in separate single-arm cohort and received BRUKINSA only. The primary endpoint was PFS per IRC in the ITT population in the BRUKINSA arm and the BR arm, with minimum 2-sided alpha of 0.05 for superiority.\(^3,4\)

Prespecified analysis assessed by IRC.\(^4\)

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

Infections (continued)

IgG antibodies 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.

Cytophenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% 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.
BRUKINSA DELIVERS POWERFUL EFFICACY IN PATIENTS WITHOUT AND WITH DEL(17p)²

Initial Analyses (30 months for PFS, 25 months for ORR)

Superior PFS: all-comer population²

PFS: patients with del(17p)²

Superior ORR: all-comer population¹

Data presented are consistent with label.² Unprespecified analysis assessed by both IRC and investigator with similar results. Median PFS has not yet been reached with BRUKINSA. Superior PFS: all-comer population²

No. of patients at risk
BRUKINSA 327 316 303 128 121 118 111 95 66 34 10 9 0
Ibrutinib 325 306 293 128 121 118 111 95 66 34 10 9 0

No. of PFS events: BRUKINSA 130 (40%); Ibrutinib 159 (49%)
HR=0.68 (95% CI: 0.53, 0.86)

Medians:
BRUKINSA 30 months
Ibrutinib 25 months

Superior ORR: all-comer population¹

No. of patients at risk
BRUKINSA 327 316 303 128 121 118 111 95 66 34 10 9 0
Ibrutinib 325 306 293 128 121 118 111 95 66 34 10 9 0

No. of PR+nPR: BRUKINSA 24 (32%); Ibrutinib 118 (36%)
CR: BRUKINSA 66 (66%); Ibrutinib 66 (66%)

No. of patients at risk
BRUKINSA 75 71 59 45 42 22 22 13 5 1 0
Ibrutinib 75 71 59 45 42 22 22 13 5 1 0

No. of events:
Non-CR: 125
CR: 66

Superior ORR: all-comer population³

Superior ORR: all-comer population³

CONSISTENT PFS vs IBRUTINIB SUSTAINED OVER 3 YEARS*²

Long-Term Analysis (~3 years)

PFS: all-comer population²

PFS: patients with del(17p)²

No. of patients at risk
BRUKINSA 327 293 273 258 247 242 236 217 206 151 124 118 88 28
Ibrutinib 325 297 287 272 258 247 242 236 217 206 151 124 118 22

No. of PFS events: BRUKINSA 31 (41%); Ibrutinib 46 (61%)
HR=0.52 (95% CI: 0.33, 0.83)

Medians:
BRUKINSA 21 months
Ibrutinib 12 months

Cardiac Arrhythmias
Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

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.

IMPORTANT SAFETY INFORMATION (continued)

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.
### Important Safety Information (continued)

#### 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 embryofetal 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.

#### Adverse Reactions in Patients without del(17p) were consistent with the established safety profile of BRUKINSA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRUKINSA (n=227)</th>
<th>BR (n=227)</th>
<th>Pooled Safety Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair loss</td>
<td>13</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Dizzy</td>
<td>14</td>
<td>13</td>
<td>13.3%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>14</td>
<td>13</td>
<td>13.3%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>10</td>
<td>10</td>
<td>10.0%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28</td>
<td>28</td>
<td>28.0%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
<td>10</td>
<td>10.0%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4</td>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>14</td>
<td>14.0%</td>
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<tr>
<td>Rash</td>
<td>25</td>
<td>22</td>
<td>22.0%</td>
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<tr>
<td>Cutaneous reaction</td>
<td>14</td>
<td>14</td>
<td>14.0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>14</td>
<td>14.0%</td>
</tr>
<tr>
<td>Nose</td>
<td>15</td>
<td>15</td>
<td>15.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>24</td>
<td>20</td>
<td>20.0%</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>14</td>
<td>14.0%</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

**Includes 3 fatal outcomes.3 Includes 3 fatal outcomes.4

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### 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.

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**Important Safety Information (continued)**

**Adverse reactions reported in a0% of patients (BRUKINSA vs ibrutinib, respectively) in the ALPINE trial included:** upper respiratory tract infection (27% vs 22%), pneumonia (18% vs 19%), COVID-19 (14% vs 10%), musculoskeletal pain (26% vs 28%), hemorrhage (24% vs 26%), hypertension (19% vs 20%), rash (20% vs 21%), bruising (16% vs 14%), diarrhea (14% vs 22%), fatigue (13% vs 14%), cough (11% vs 11%), and dizziness (10% vs 7%).5

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### 2L: ALPINE

#### Initial Analysis: Lower rates of cardiac events including atrial fibrillation and no cardiac deaths vs ibrutinib2,5

- **Cardiac adverse events**: 69 (21.3%) vs 96 (29.6%)
- **Cardiac serious adverse events**: 6 (1.9%) vs 25 (7.7%)
- **Cardiac adverse events leading to treatment discontinuation**: 1 (0.3%) vs 14 (4.3%)
- **Cardiac fatal events**: 0 (0%) vs 6 (1.9%)

*BRUKINSA cardiac-related discontinuation in 1 patient was for ventricular extrasystoles. ibrutinib cardiac-related discontinutions were for atrial fibrillation (1), cardiac arrest (2), cardiac failure (2), cardiac failure acute (1), congestive cardiomyopathy (1), myocardial infarction (1), palpitations (1), and ventilator failure (1).1

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**There were no new safety signals at ~4 years with BRUKINSA1**

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**IMPORTANT SAFETY INFORMATION (continued)**

**DRUG INTERACTIONS**

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**ADVERSE REACTIONS**

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≤0% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrage (30%), and musculoskeletal pain (30%).

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**DRUG INTERACTIONS**

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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.

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.

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.

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% 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.

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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 accompanying full Prescribing Information, including Patient Information.


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