First- and second-generation BTK inhibitors

A guide to **drug interactions**, **dosing modifications**, and **access support**

Brukinsa®
zanubrutinib 160 mg tablets

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.
- Relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy.

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

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Please see Important Safety Information on pages 8-9 and full **Prescribing Information**.

Introduction

Bruton tyrosine kinase (BTK) inhibitors are the standard of care for treatment of patients with B-cell malignancies. **First-generation Imbruvica® (ibrutinib)** has established efficacy; however, significant adverse reactions and drug-drug interaction risks are documented. **Second-generation inhibitors**, such as **Calquence® (acalabrutinib) and BRUKINSA® (zanubrutinib)**, offer improved selectivity, reduced off-target effects, and improved tolerability.[1] This resource is designed to aid in **decision-making** to **optimize patient outcomes** and **streamline access.**

This is an interactive resource.

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SUMMARY

	BRUKINSA (zanubrutinib)[2]	**Calquence** (acalabrutinib)[3]	**Imbruvica** (ibrutinib)[4]
Dosing flexibility	✓ **Flexible dosing** (only BTK inhibitor with once- or twice-daily options)	✗ **Fixed dosing** (no once-daily option)	✗ **Fixed dosing** (no twice-daily option)
CYP3A drug–drug interactions *(inhibitors/inducers)*	✓ **Manageable**	± **Partial flexibility**	✗ **Restrictive**
Hepatic impairment	✓ **Child-Pugh A (mild) or B (moderate) liver impairment** (no dose modification) ✓ **Child-Pugh C (severe)** (reduce dose to 80 mg twice daily)	✓ **Child-Pugh A (mild) or B (moderate) liver impairment** (no dose modification) ✗ **Child-Pugh C (severe)** (contraindicated)	✓ **Child-Pugh A (mild) liver impairment** (reduce to 140 mg once daily; one-third of standard dose) ✓ **Child-Pugh B (moderate) liver impairment** (reduce to 70 mg once daily; one-sixth of standard dose) ✗ **Child-Pugh C (severe)** (avoid use; limited data)
Bleeding risks *and anticoagulation*	± **Warfarin** (*no clinically significant PK interaction observed with warfarin*) ± **Antiplatelets/anticoagulants** (concomitant therapy may increase bleed risk) ± **P-glycoprotein (P-gp) interactions** (substrate of P-gp; *no clinically meaningful effect noted*)	± **Warfarin** (not studied) ± **Antiplatelets/anticoagulants** (*any* antithrombotic therapy can increase bleeding; **generally avoid vitamin K antagonists**) ✓ **P-gp interactions** (substrate of P-gp; no known P-gp–mediated drug-drug interactions)	✗ **Warfarin** (higher rates of major bleeds with anticoagulants) ✗ **Anticoagulants/antiplatelets** (any concomitant use increases major bleeds) ✗ **P-gp interactions** (inhibits P-gp; increases exposure of P-gp substrates)

Data presented are consistent with prescribing information.

Abbreviation: PK, pharmacokinetic.

Please see Important Safety Information on pages 8-9 and full Prescribing Information.

BTK inhibitor class overview

	BRUKINSA (zanubrutinib)[2]	**Calquence** (acalabrutinib)[3]	**Imbruvica** (ibrutinib)[4]
Manufacturer	**BeOne Medicines**	**AstraZeneca**	**Pharmacyclics**
Generation	**Second**	**Second**	**First**
B-cell lymphoma indications[a]	**TN and R/R CLL/SLL** **TN and R/R WM** **R/R MCL** **R/R MZL** **R/R FL** (in combination with obinutuzumab, after ≥2 lines of systemic therapy)	**TN and R/R CLL/SLL** **TN and R/R MCL**	**TN and R/R CLL/SLL** **TN and R/R WM**
Dosing regimen	**Flexible dosing** 160 mg twice daily or 320 mg once daily	**Twice-daily dosing** 100 mg every 12 hours	**Once-daily dosing** 420 mg once daily
How supplied	**160-mg scored tablets, 60 tablets per bottle** NDC 72579-0122-01	**100-mg tablets, 60 tablets per bottle** NDC 0310-3512-60	**70-mg capsules, 28 capsules per bottle** NDC 57962-0070-28 **140-mg capsules, 90 capsules per bottle** NDC 57962-0140-09 **120 capsules per bottle** 57962-0140-12 **All tablet packaging configurations:** one folded blister card containing two 14-count blister strips for a total of 28 tablets **140-mg tablets** NDC 57962-0014-28 **280-mg tablets** NDC 57962-0280-28 **420-mg tablets** NDC 57962-0420-28
Key considerations	**Flexible dosing** and **scored tablet** formulation offer convenience and adaptability. BRUKINSA can be taken once or twice daily, allowing personalization to patient needs and tolerability. This flexibility may help support adherence and simplify dose management.	**Only a fixed twice-daily dosing option** is available, which limits flexibility and may pose adherence challenges.	**Once-daily dosing with no scored or divisible option available,** limiting flexibility and options for managing adherence or tolerability between prescription fills.

BRUKINSA tablets have replaced capsules. This formulation provides the same flexibility and convenience of taking BRUKINSA that patients know, and based on bioequivalence, the same efficacy and safety can be expected.

Data presented are consistent with prescribing information.

[a]BTK inhibitors were evaluated for the following indications only: MCL, MZL, WM, and CLL/SLL. BTK inhibitors may have other indications not included in this class review.

Abbreviations: NDC, National Drug Code; R/R, relapsed/refractory; TN, treatment naive.

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Drug-drug and hepatic dosage modifications

All BTK inhibitors **are metabolized by CYP3A4** and concomitant administration with CYP3A inhibitors or inducers is a key concern[2-4]

Recommendations for Use With CYP3A Inhibitors or Inducers

Coadministered Drug	**BRUKINSA** (zanubrutinib)[2]	**Calquence** (acalabrutinib)[3]	**Imbruvica** (ibrutinib)[4,a]
Strong CYP3A inhibitor	**80 mg once daily**	**Avoid concomitant use** If these inhibitors will be used short term (such as anti-infectives for up to seven days), interrupt acalabrutinib	**Avoid concomitant use** If these inhibitors will be used short term (such as anti-infectives for up to seven days), interrupt ibrutinib
Moderate CYP3A inhibitor	**80 mg twice daily**	**100 mg once daily**	**280 mg once daily**
Strong CYP3A inducer	**Avoid concomitant use**	**Avoid concomitant use** If these inducers cannot be avoided, increase dose to 200 mg approximately every 12 hours	**Avoid concomitant use**
Moderate CYP3A inducer	**Avoid concomitant use** If these inducers cannot be avoided, consider dose increase up to 320 mg twice daily based on tolerability	**No dose modifications are required**	**No dose modifications are required**

[a]If ibrutinib is coadministered with voriconazole 200 mg twice daily or posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily, the recommended dose of ibrutinib is 140 mg once daily. If ibrutinib is coadministered with posaconazole 200 mg three times daily or 400 mg twice daily, posaconazole intravenously 300 mg once daily, or posaconazole delayed-release tablets 300 mg once daily, the recommended dose of ibrutinib is 70 mg once daily.[4]

Dosage Recommendations for Use in Hepatic Impairment

Child-Pugh Score	**BRUKINSA** (zanubrutinib)[2]	**Calquence** (acalabrutinib)[3]	**Imbruvica** (ibrutinib)[4]
Class A	**No dose modifications are required**	**No dose modifications are required**	**140 mg once daily**
Class B	**No dose modifications are required**	**No dose modifications are required**	**70 mg once daily**
Class C	**80 mg twice daily**	**Avoid concomitant use**	**Avoid concomitant use**

BRUKINSA is the ***only BTK inhibitor*** that can be **used in severe hepatic impairment**[2-4]

- **No dose modification** for patients with mildly to moderately impaired kidney or liver function
- **Dose adjustment** recommended in patients with severely impaired liver function

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 adverse reactions in patients with hepatic impairment.[2]

Data presented are consistent with prescribing information.

Please see Important Safety Information on pages 8-9 and full Prescribing Information.

Patient-specific dosage modifications

All BTK inhibitors **inhibit platelet function** to some extent (class effect of BTK in platelets)

Anticoagulant and Bleeding Risk Across BTK Inhibitors

	BRUKINSA (zanubrutinib)[2]	**Calquence** (acalabrutinib)[3]	**Imbruvica** (ibrutinib)[4]
Warfarin	PI warns of additive bleeding risk; no clinically significant PK interaction observed with warfarin	Warfarin not specifically studied; PI states *any* antithrombotic therapy can increase bleeding; **generally avoid vitamin K antagonists** and weigh risk/benefit carefully	**PI notes higher rates of major bleeds with anticoagulants; avoid vitamin K antagonists where possible** and monitor closely if no alternative
Other cautions	**Bleeding risk increases with dual antiplatelet/anticoagulant therapy** **Withhold 3 to 7 days pre- and post surgery** depending on bleed risk	**Withhold 3 to 7 days pre- and post surgery** depending on bleed risk Monitor if any antithrombotic agent is added	**Major hemorrhage risk increases with any antiplatelet or anticoagulant** (eg, NSAIDs, fish oil); clinical judgment advised for elective procedures
P-gp interaction	**Substrate of P-gp; coadministration increases digoxin C_{max} 34%/AUC 11%;** *no clinically meaningful effect noted*	**Substrate of P-gp; not an inhibitor;** *no known P-gp–mediated drug-drug interactions*	**Inhibits P-gp and BCRP in vitro; may increase exposure of P-gp substrates (eg, digoxin);** *close monitoring recommended*

BRUKINSA demonstrates lower incidence of atrial fibrillation and reduced cardiac risk compared with ibrutinib; BRUKINSA demonstrated lower incidence of atrial fibrillation compared with ibrutinib in CLL and WM populations in two phase 3 clinical trials—ALPINE (5.2% vs 13.3%) and ASPEN (7.9% vs 23.5%), respectively.[2,4–6]

Data presented are consistent with prescribing information.

Abbreviations: AUC, area under the curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma drug concentration; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; PI, prescribing information; PK, pharmacokinetic.

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Treatment choice and access implications

MARKET ACCESS TRENDS

Highlighting drug-drug interaction profiles can effectively support prior authorization approvals and appeals by clearly demonstrating the medical necessity and potential risk mitigation associated with specific BTK inhibitors.

Formularies that prioritize one BTK inhibitor may unintentionally **elevate patient risk** due to unrecognized drug-drug interactions. **Individualized medication assessments** and **comprehensive patient histories** are crucial to identify and mitigate these risks.

Emerging payer trends increasingly consider **real-world evidence (RWE)** and **health economics outcomes research (HEOR)** data to guide formulary decisions; emphasizing clinical data that support safer and more effective treatment options can positively influence formulary inclusion and positioning.

ROLE OF PHARMACISTS

Pharmacists are uniquely positioned to proactively manage treatment regimens by conducting comprehensive medication reviews and monitoring for drug-drug interactions, thereby preventing adverse events and optimizing therapeutic outcomes.

Pharmacists also play a **key advocacy role,** assisting in the preparation of robust prior authorization documentation and appeals, particularly **highlighting medication safety, tolerability, and clinical necessity.**

Collaborative efforts between pharmacists and healthcare providers can streamline the authorization process, enhance patient compliance, and ultimately improve patient access and clinical outcomes.

Please see Important Safety Information on pages 8-9 and full Prescribing Information.

Access optimization for BRUKINSA[2-4]

Optimizing outcomes through individualized treatment selection

- BRUKINSA emerges as a **viable BTK inhibitor** for patients requiring enhanced safety profiles, particularly those susceptible to **drug-drug interactions, anticoagulant use, and bleeding risks.**
- By offering improved selectivity, BRUKINSA may reduce potential complications associated with concomitant medications and complex clinical scenarios.

Ideal for patients with high drug-drug interaction risk

- Patients frequently requiring medications metabolized through **CYP3A4 pathways** will particularly benefit from BRUKINSA's lower interaction profile.
- **Simple dose adjustment** for coadministration with strong or moderate CYP3A inhibitors. Coadministration with mild CYP3A inducers should be done with caution.

Reduced cardiac and bleeding risks

- BRUKINSA presents **fewer cardiac risks** and a notably **lower bleeding risk** compared with first-generation BTK inhibitor, ibrutinib.[5]
- This is especially advantageous for patients with **preexisting cardiac conditions or those concurrently receiving anticoagulants or antiplatelet therapies**, for whom minimizing bleeding risks is crucial.

Offers unmatched dosing flexibility

- BRUKINSA is the ***only*** BTK inhibitor that **offers the choice of two dosing schedules.**
- BRUKINSA is the ***only*** BTK inhibitor that can be used in **severe hepatic impairment.**
- **No dosage modification** for patients with mildly to moderately impaired kidney or liver function.

Straightforward dosage modifications

- BRUKINSA offers more flexibility with **straightforward dosage modifications for ≥ Grade 3 adverse reactions.**
- **Simply reduce the number of or split** the BRUKINSA tablets in half as prescribed by the healthcare provider.
- BRUKINSA does **not require a new prescription or dose exchange** for dose reductions.

Data presented are consistent with prescribing information.

Please see Important Safety Information on pages 8-9 and full Prescribing Information.

Brukinsa® 160 mg zanubrutinib tablets

Important safety information

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.8% of patients treated with BRUKINSA in clinical trials, with fatalities occurring in 0.2% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 32% 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 before and after 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. Grade 3 or higher infections occurred in 26% of patients, most commonly pneumonia (7.9%), with fatal infections occurring in 3.2% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, *pneumocystis jirovecii* 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 (21%), thrombocytopenia (8%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA. Grade 4 neutropenia occurred in 10% of patients, and Grade 4 thrombocytopenia occurred in 2.5% 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.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA. The most frequent second primary malignancy was non-melanoma skin cancers (8%), followed by other solid tumors in 7% of the patients (including melanoma in 1% of patients) and hematologic malignancies (0.7%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 4.4% of patients treated with BRUKINSA, including Grade 3 or higher cases in 1.9% 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 0.3% 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.

Important safety information (cont)

WARNINGS AND PRECAUTIONS (CONT)

Hepatotoxicity, Including Drug-Induced Liver Injury

Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), has occurred in patients treated with Bruton tyrosine kinase inhibitors, including BRUKINSA.

Evaluate bilirubin and transaminases at baseline and throughout treatment with BRUKINSA. For patients who develop abnormal liver tests after BRUKINSA, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold BRUKINSA. Upon confirmation of DILI, discontinue BRUKINSA.

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.

ADVERSE REACTIONS

The most common adverse reactions (≥30%), including laboratory abnormalities, in patients who received BRUKINSA (N=1729) are decreased neutrophil count (51%), decreased platelet count (41%), upper respiratory tract infection (38%), hemorrhage (32%), and musculoskeletal pain (31%).

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 full Prescribing Information.

Key takeaways

BRUKINSA offers enhanced selectivity, fewer drug-drug interactions, and reduced cardiac risk versus first-generation BTK inhibitor, ibrutinib[1,2,4]

Strategic medication assessments and documentation enhance patient access and streamline approval processes

Pharmacists' involvement in monitoring and documentation supports successful access optimization

myBeOneSupport™

Reimbursement information and support are just a call away. Call 1-833-234-4363

Oncology Nurse Advocates are available Monday through Friday from 8 AM to 8 PM ET

To learn more about BRUKINSA and all its indications, visit **www.BRUKINSA.com**

References: 1. Tam C, Thompson PA. BTK inhibitors in CLL: second-generation drugs and beyond. *Blood Adv.* 2024;8(9):2300-2309. doi:10.1182/bloodadvances.2023012221 **2.** BRUKINSA. Package insert. BeOne Medicines USA, Inc.; 2025. **3.** Calquence. Package insert. AstraZeneca Pharmaceuticals LP; 2025. **4.** Imbruvica. Package insert. Pharmacyclics LLC, Janssen Biotech, Inc; 2024. **5.** Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388(4):319-332. doi:10.1056/NEJMoa2211582 **6.** Dimopoulos MA, Opat S, D'Sa S, et al. Zanubrutinib versus ibrutinib in symptomatic Waldenström macroglobulinemia: final analysis from the randomized phase III ASPEN study. *J Clin Oncol.* 2023;41(33):5099-5106. doi:10.1200/JCO.22.02830

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Brukinsa® zanubrutinib 160 mg tablets