Adverse Event Management Guide for CALQUENCE + BR

1L MCL

Tips for helping your patients manage certain adverse reactions with CALQUENCE when used in combination with bendamustine and rituximab[1]

Advise patients to inform you if they experience any of these adverse reactions associated with CALQUENCE, or others.[1] (Please see back cover.)

Rash[2]

- Recommend treatments such as topical therapies, antihistamines, and mild soaps to manage severe or persistent symptoms
- Advise patients to avoid scratching the rash to help prevent risk of infection and bleeding
- Recommend sun protection to help prevent the rash from worsening

Diarrhea[3,4]

- Advise patients to drink clear liquids such as water or oral rehydration drinks to replace lost fluids and electrolytes
- Advise patients to eat smaller, more frequent, low-fiber meals
- Grade 1 or 2 diarrhea may be managed at home with an antidiarrheal medication

Fatigue[5]

- Advise patients to get adequate nighttime sleep and take short naps early in the day
- Recommend relaxation and stress reduction through enjoyable activities or moderate exercise like walking (advise patients to consult their primary healthcare provider before starting any exercise plan)

Headache[6,7]

- Cancer treatment-induced headaches that are mild can be effectively managed with acetaminophen or caffeine
- If headache is severe, advise patients to seek emergency care for evaluation

Vomiting[8]

- Recommend treatment options to prevent and control vomiting, such as antiemetics and steroids
- Advise patients to sip liquids slowly throughout the day to prevent dehydration

The most common adverse reactions (≥30%), excluding laboratory abnormalities, of patients treated with CALQUENCE are diarrhea, upper respiratory tract infection, headache, musculoskeletal pain, lower respiratory tract infection, and fatigue.[1] (Please see page 2 for additional safety data.)

1L=first-line; auto-HSCT=autologous hematopoietic stem cell transplantation; BR=bendamustine + rituximab; MCL=mantle cell lymphoma.

INDICATION AND USAGE

CALQUENCE is a Bruton tyrosine kinase (BTK) inhibitor indicated in combination with bendamustine and rituximab (BR) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation (HSCT).

IMPORTANT SAFETY INFORMATION ABOUT CALQUENCE® (acalabrutinib) tablets

Serious and Opportunistic Infections

Fatal and serious infections, including opportunistic infections, have occurred in patients with hematologic malignancies treated with CALQUENCE.

Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 29% of 2,055 patients exposed to CALQUENCE in clinical trials, most often due to respiratory tract infections (18% of all patients, including pneumonia in 14%). These infections predominantly occurred in the absence of Grade 3 or 4 neutropenia, with neutropenic infection reported in 8% of all patients. Opportunistic infections in recipients of CALQUENCE have included, but are not limited to, hepatitis B virus reactivation, fungal pneumonia, *Pneumocystis jirovecii* pneumonia, Epstein-Barr virus reactivation, cytomegalovirus, and progressive multifocal leukoencephalopathy (PML). Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly.

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients treated with CALQUENCE. Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 4.7% of patients, with fatal hemorrhage occurring in 0.1% of 2,055 patients exposed to CALQUENCE in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 39% of patients.

Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. In clinical trials, major hemorrhage occurred in 5% of patients taking CALQUENCE without antithrombotic agents and 3.2% of patients taking CALQUENCE with antithrombotic agents. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding.

Consider the benefit-risk of withholding CALQUENCE for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cytopenias

CALQUENCE can cause Grade 3 or 4 cytopenias. Grade 3 or 4 cytopenias included absolute neutrophil count decreased (28%), absolute lymphocyte count decreased (10%), hemoglobin decreased (9%), and platelets decreased (9%) in 1,758 patients treated with CALQUENCE alone and in combination with obinutuzumab or venetoclax; Grade 4 neutropenia developed in 14% of patients.

Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted.

Second Primary Malignancies

Second primary malignancies, including skin cancers and other solid tumors, occurred in 16% of 2,055 patients exposed to CALQUENCE in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 9% of patients, followed by other solid tumors in 8% (including melanoma, lung cancer, gastrointestinal cancers, and genitourinary cancers) and hematologic malignancies (1.1%). Fatal second primary malignancies occurred in 0.8% of patients. Monitor patients for the development of second cancers and advise protection from sun exposure.

Please see Important Safety Information throughout, and full Prescribing Information, including Patient Information.

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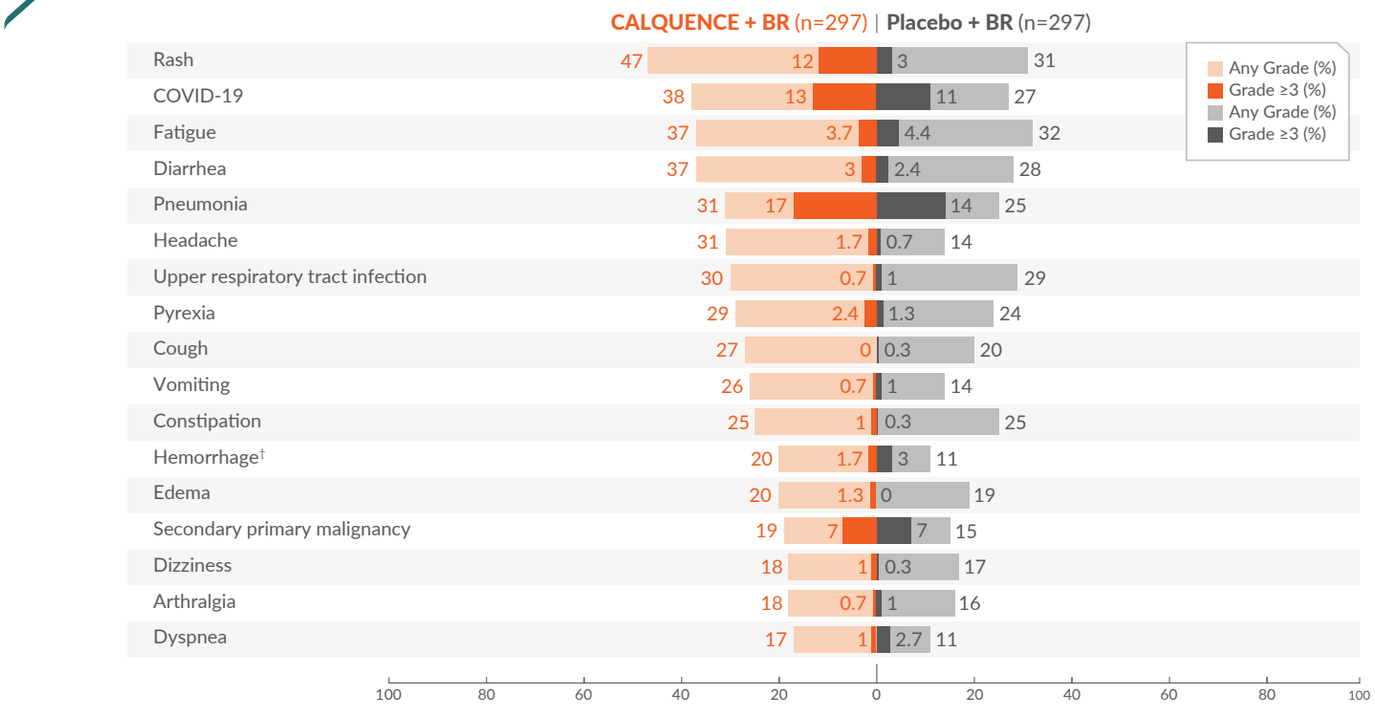
Safety was consistent with the established profile of CALQUENCE*[1,9]

Most adverse reactions were Grade 1 or 2 in the CALQUENCE + BR arm

Most common ARs in the ECHO trial



Values >5 are rounded to the nearest whole number.

- The median duration of exposure was 28.6 months with CALQUENCE + BR and 24.6 months with placebo + BR[1,10]
- Grade 4 laboratory abnormalities in >15% of patients treated with CALQUENCE + BR include absolute lymphocyte count decreased (26%), absolute neutrophil count decreased (36%), and uric acid increased (17%)[1]

*Except COVID-19.[9]
†Hemorrhage includes all terms containing hematoma, hemorrhage, and related terms indicative of bleeding.[1]
ARs=adverse reactions.

Safety and tolerability profile[1]

- Serious adverse reactions occurred in 69% of patients who received CALQUENCE + BR. Serious adverse reactions reported in ≥2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia), pyrexia (6%), second primary malignancy (7%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%)
- Fatal ARs that occurred within 30 days of the last study treatment were reported in 12% of patients who received CALQUENCE + BR, including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), sepsis (0.3%), second primary malignancy (0.7%), and pneumonitis (0.3%)

Serious and Opportunistic Infections:

- Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat promptly; Inform patients of the possibility of serious infection and to report signs or symptoms suggestive of infection

Cytopenias:

- Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted; Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE

Cardiac Arrhythmias:

- The risk of arrhythmias may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (eg, palpitations, dizziness, syncope, dyspnea) and manage as appropriate; Counsel patients to report any signs of palpitations, dizziness, fainting, chest discomfort, and shortness of breath

Hemorrhage:

- Use of antithrombotic agents concomitantly with CALQUENCE may further increase the risk of hemorrhage. Consider the risks and benefits of antithrombotic agents when co-administered with CALQUENCE. Monitor patients for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding; Inform patients to report signs or symptoms of bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries

Second Primary Malignancies:

- Monitor patients for the development of second cancers and advise protection from sun exposure; Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer and other solid tumors. Advise patients to use sun protection

Hepatotoxicity:

- Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE. For patients who develop abnormal liver tests after CALQUENCE, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold CALQUENCE. Upon confirmation of DILI, discontinue CALQUENCE. Advise patients to contact their healthcare provider immediately if they experience abdominal discomfort, dark urine, or jaundice

DILI=drug induced liver injury.

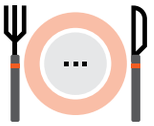
Please see Important Safety Information throughout, and full Prescribing Information, including Patient Information.

Dosage and administration instructions[1]

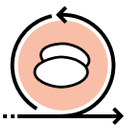
No PPI restrictions with tablet formulation[1]

CALQUENCE administration instructions[1]

Tablet should be swallowed whole with water; do not chew, crush, dissolve, or cut



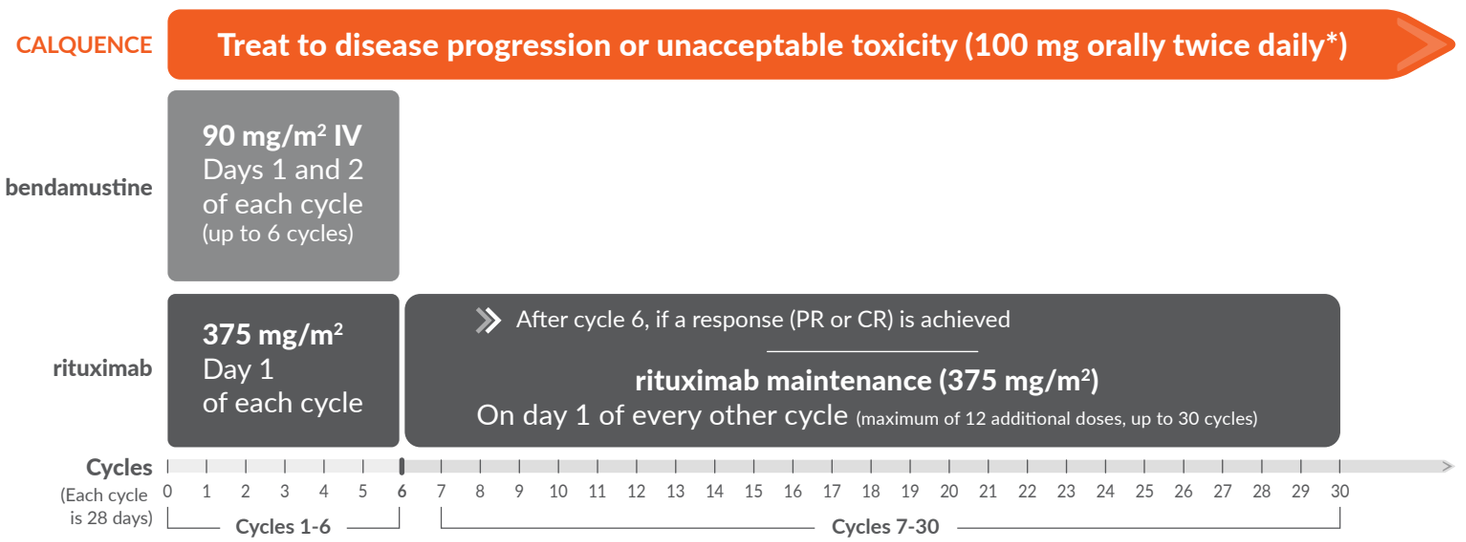
Can be taken with or without food



One 100 mg tablet taken orally, twice daily*

If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped, and the next dose should be taken at its regularly scheduled time. Extra tablets of CALQUENCE should not be taken to make up for a missed dose.

For patients with previously untreated MCL[1]



*Approximately every 12 hours.[1]
CR=complete response; PPI=proton pump inhibitor; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)

Cardiac Arrhythmias
Fatal and serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. Grade 3 or 4 atrial fibrillation or flutter was reported in 2.2% of 2,055 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 7% of all patients. Grade 3 or higher ventricular arrhythmia events were reported in 0.5% of patients, including fatal cases in 0.3% of all patients. The risk of arrhythmias may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (eg, palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

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 CALQUENCE.

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

ADVERSE REACTIONS
Previously Untreated Mantle Cell Lymphoma
The most common adverse reactions (≥15%) of any grade in patients with previously untreated MCL in the ECHO study who received CALQUENCE plus BR (n=297) were rash (47%), COVID-19 (38%), fatigue (37%), diarrhea (37%), pneumonia (31%), headache (31%), upper respiratory tract infection (30%), pyrexia (29%), cough (27%), vomiting (26%), constipation (25%), hemorrhage (20%), edema (20%), secondary primary malignancy (19%), dizziness (18%), arthralgia (18%), and dyspnea (17%).

Grade 4 laboratory abnormalities in >15% of patients treated with CALQUENCE plus BR include absolute lymphocyte count decreased (26%), absolute neutrophil count decreased (36%), and uric acid increased (17%).

Serious adverse reactions occurred in 69% of patients who received CALQUENCE plus BR. Serious adverse reactions reported in ≥2% of patients were pneumonia (23%; includes COVID-19 pneumonia), COVID-19 (20%; includes COVID-19 pneumonia), second primary malignancy (7%), pyrexia (6%), rash (3.4%), febrile neutropenia (3.4%), atrial fibrillation (3%), sepsis (2.7%), and anemia (2.4%). Fatal adverse reactions that occurred within 30 days of the last study treatment were reported in 12% who received CALQUENCE plus BR including COVID-19 (6%; includes COVID-19 pneumonia), pneumonia (1%), second primary malignancy (0.7%), sepsis (0.3%), and pneumonitis (0.3%).

Adverse reactions led to permanent discontinuation of CALQUENCE in 43%, dosage interruptions in 74%, and dosage reductions in 10% of patients. Adverse reactions that resulted in dosage modification in >10% included infections, cytopenias, rashes, and gastrointestinal toxicity. Adverse reactions which resulted in permanent discontinuation of CALQUENCE in ≥4% of patients included COVID-19 (includes COVID-19 pneumonia) and neutropenia.

DRUG INTERACTIONS
Strong CYP3A Inhibitors: Avoid co-administration of CALQUENCE with a strong CYP3A inhibitor. If these inhibitors will be used short-term, interrupt CALQUENCE. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE.

Moderate CYP3A Inhibitors: Reduce the dosage of CALQUENCE to 100 mg once daily when co-administered with a moderate CYP3A inhibitor.

Strong CYP3A Inducers: Avoid co-administration of CALQUENCE with a strong CYP3A inducer. If co-administration is unavoidable, increase the dosage of CALQUENCE to 200 mg approximately every 12 hours.

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Recommended dosage modifications for adverse reactions with CALQUENCE + BR[1]

ARs	Severity*	Dosage Modification (Starting dosage of CALQUENCE: 100 mg approximately every 12 hours)
Neutropenia†	Absolute neutrophil count less than 0.5 x 10^9/L for greater than 7 days	• Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤2, resume CALQUENCE at starting dosage • Upon second or third occurrence, reduce dosage of CALQUENCE to 100 mg once daily‡ • Discontinue CALQUENCE at fourth occurrence For bendamustine†: Interrupt bendamustine. Once toxicity has resolved to Grade ≤2, resume bendamustine and consider dosage reduction to 70 mg/m^2.§‖
Thrombocytopenia¶	Platelet count 25 to 50 x 10^9/L with clinically significant bleeding or platelet count less than 25 x 10^9/L	• Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤2 or baseline, resume CALQUENCE at starting dosage • If recurrence, reduce dosage of CALQUENCE to 100 mg once daily‡ • Consider discontinuing CALQUENCE at third occurrence For bendamustine¶: Interrupt bendamustine. Once toxicity has resolved to Grade ≤2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.‖
Nonhematologic adverse reactions	Grade 3 or higher	• Interrupt CALQUENCE. Once toxicity has resolved to Grade ≤2 or baseline, resume CALQUENCE at starting dosage • If recurrence, reduce dosage of CALQUENCE to 100 mg once daily‡ • Discontinue CALQUENCE at third occurrence of Grade 4 toxicity. For Grade 3 toxicity, consider the risks and benefits of continuing CALQUENCE For bendamustine: Interrupt bendamustine. Once toxicity has resolved to Grade ≤2 or baseline, resume bendamustine and consider dose reduction to 70 mg/m^2.‖

Refer to the Prescribing Information of each of the products used in combination with CALQUENCE for additional information for management of toxicities.

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.[1]
†For neutropenia with ANC less than 1 x 10^9/L, consideration for bendamustine dose interruption and dosage reduction to 70 mg/m^2 may be appropriate in certain circumstances.[1]
‡Dose may be re-escalated at the discretion of the physician if patient tolerates a reduced dose for ≥4 weeks.[1]
§Consider use of myeloid growth factors before bendamustine dosage reduction.[1]
‖Consider discontinuing bendamustine if additional dosage reduction is required.[1]
¶For thrombocytopenia, a platelet count below 50 x 10^9/L should prompt bendamustine dose interruption even in the absence of clinically significant bleeding.[1]
ANC=absolute neutrophil count.

IMPORTANT SAFETY INFORMATION (cont'd)

SPECIFIC POPULATIONS

Based on findings in animals, CALQUENCE may cause fetal harm and dystocia when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

Pregnancy testing is recommended for females of reproductive potential prior to initiating CALQUENCE therapy. Advise female patients of reproductive potential to use effective contraception during treatment with CALQUENCE and for 1 week following the last dose of CALQUENCE.

It is not known if CALQUENCE is present in human milk. Advise lactating women not to breastfeed while taking CALQUENCE and for 2 weeks after the last dose.

Avoid use of CALQUENCE in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

SCAN FOR FULL PRESCRIBING INFORMATION

Please see Important Safety Information throughout, and full Prescribing Information, including Patient Information.

You may report side effects related to AstraZeneca products.

References: 1. CALQUENCE® (acalabrutinib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2026. **2.** American Cancer Society. Rashes and skin changes. https://www.cancer.org/cancer/managing-cancer/side-effects/hair-skin-nails/rashes-skin-changes.html. Updated September 12, 2024. Accessed March 3, 2026. **3.** Diarrhea. NIH MedlinePlus. https://medlineplus.gov/diarrhea.html#summary. Updated June 1, 2025. Accessed March 3, 2026. **4.** NIH National Cancer Institute. Diarrhea and cancer treatment. https://www.cancer.gov/about-cancer/treatment/side-effects/diarrhea. Updated May 16, 2025. Accessed March 3, 2026. **5.** American Cancer Society. Cancer-related fatigue. https://www.cancer.org/content/dam/CRC/PDF/Public/7799.00.pdf. Updated July 16, 2024. Accessed March 3, 2026. **6.** O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and managing BTK inhibitor treatment-related adverse events in clinical practice. *Front Oncol*. 2021;11:720704. **7.** NIH. National Cancer Institute: NCI-CONNECTions. Headache. https://www.cancer.gov/rare-brain-spine-tumor/living/symptoms/headache. Updated March 17, 2024. Accessed March 3, 2026. **8.** American Cancer Society. Nausea and vomiting. https://www.cancer.org/content/dam/CRC/PDF/Public/9546.00.pdf. Updated June 26, 2024. Accessed March 3, 2026. **9.** Wang M, Mayer J, Belada D, et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma (MCL): results from the phase 3, double-blind, placebo-controlled ECHO trial. Presented at: European Hematology Association (EHA) annual meeting; June 13-16, 2024; Madrid, Spain. **10.** Data on File. REF-255868. AstraZeneca Pharmaceuticals LP.

CALQUENCE® acalabrutinib 100 mg tablets