Drug Monograph

A - Drug Name

acalabrutinib

COMMON TRADE NAME(S): Calquence®

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B - Mechanism of Action and Pharmacokinetics

Acalabrutinib is a highly selective, potent small-molecule Bruton's tyrosine kinase (BTK) inhibitor that prevents B-cell activation and signaling.

Absorption	Bioavailability	25%; acalabrutinib tablets and capsules have equivalent oral bioavailability except when co-administered with acid reducing agents
	Effects with food	Food is unlikely to have clinically important effects. Administration with acidic beverages, such as orange juice and grapefruit juice, decreased AUC of the **capsules** by 40% and 17%, respectively.
	Peak plasma levels	**Tablets:** 0.5 hours (acalabrutinib), 0.75 hours (ACP-5862) **Capsules:** 0.9 hours (acalabrutinib), 1.6 hours (ACP-5862)

Distribution	PPB	97.5% (acalabrutinib) and 98.6% (ACP-5862)
	Cross blood brain barrier?	Unknown
Metabolism	Acalabrutinib is primarily metabolized by CYP3A enzymes, and to a minor extent by glutathione conjugation and amide hydrolysis.	
	Active metabolites	Yes (ACP-5862)
Elimination	Feces	84% (<2% as unchanged drug)
	Urine	12% (<2% as unchanged drug)
	Half-life	**Tablets:** terminal half-life: 1.4 hours (acalabrutinib); 6.6 hours (ACP-5862) **Capsules:** terminal half-life: 1 hour (acalabrutinib); 3.5 hours (ACP-5862)

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C - Indications and Status

Health Canada Approvals:

- Chronic lymphocytic leukemia (CLL).
- Mantle cell lymphoma (MCL)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were reported in ≥ 5% of patients in a Phase III study of previously untreated CLL patients. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (4%) (may be severe)	E
	Hypertension (5%)	E
Dermatological	Rash (19%)	E
Gastrointestinal	Constipation (11%)	E
	Diarrhea (35%)	E
	Nausea, vomiting (22%) (generally mild)	E
General	Edema (9%) (peripheral)	E
	Fatigue (18%)	E
Hematological	Hemorrhage (39%) (2% severe)	E
	Myelosuppression (16%) (may be severe)	E
Hepatobiliary	↑ LFTs (20%)	E
Infection	Infection (65%) (may be severe)	E
Metabolic / Endocrine	Hyperuricemia (22%)	E
	Tumor lysis syndrome (1%) (CLL)	I
Musculoskeletal	Musculoskeletal pain (32%)	E
Neoplastic	Secondary malignancy (8%) (6% non-melanoma skin)	D L
Nervous System	Dizziness (12%)	E
	Headache (37%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for acalabrutinib include infection, bleeding, headache, diarrhea, musculoskeletal pain, hyperuricemia, nausea, vomiting, ↑ LFTs, rash and fatigue.

Atrial fibrillation or atrial flutter were reported in 4% of patients, including Grade 3 events in 1% of patients. Patients with severe cardiovascular disease were excluded from clinical trials.

Second primary malignancies, including skin and other solid tumours, have been reported. The most frequent was non-melanoma skin cancer (6%).

Grade 3 or 4 **myelosuppression**, including neutropenia, anemia, and thrombocytopenia have occurred during treatment, and should be monitored.

A temporary increase in lymphocyte counts (≥50% from baseline and a post baseline assessment ALC ≥5 x 10^9 /L) has occurred in 54% of patients, upon initiation of treatment. The median time to onset and duration of **lymphocytosis** were 1 week and 7 weeks, respectively.

Serious hemorrhagic events have occurred in patients with (4%) and without (3%) concomitant antithrombotic agents. Patients who were receiving warfarin or other vitamin K antagonists or who had a recent history of stroke or intracranial hemorrhage were excluded from clinical trials.

Serious infections, including fatal, have been reported. **Pneumonia** was the most frequent. Progressive multifocal leukoencephalopathy (PML) and infections due to hepatitis B virus (HBV) reactivation have been reported. Opportunistic infections, such as aspergillosis, fungal pneumonia, and Pneumocystis Jiroveci Pneumonia (PJP), have also occurred.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Acalabrutinib is affected by CYP3A inducers and inhibitors; see Drug Interaction section for dose adjustments.

Consider the benefit-risk analysis of withholding acalabrutinib for at least 3 days pre-and post-surgery due to bleeding risk.

Consider prophylaxis for tumour lysis syndrome (TLS) in patients at higher risk of TLS (e.g. first cycle in patients with CLL).

Consider prophylaxis in patients at increased risk for opportunistic infections (e.g. aspergillosis, fungal pneumonia, and Pneumocystis Jiroveci Pneumonia).

Adults:

Acalabrutinib tablets and capsules are bioequivalent and have equivalent oral bioavailability **except** when co-administered with acid reducing agents. (Refer to Interactions section.)

Oral: 100 mg BID

Dosage with Toxicity:

Dose Level	Acalabrutinib Dose
0	100 mg BID
-1	100 mg Daily
-2	Discontinue

Toxicity	Occurrence	Action
Grade ≥ 3 non-hematologic toxicities OR Grade 3 thrombocytopenia with significant bleeding OR Grade 4 thrombocytopenia OR Grade 4 neutropenia lasting longer than 7 days	First and second	Hold until toxicity is Grade 1 or baseline. Resume at same dose.
	Third	Hold until toxicity is Grade 1 or baseline. Resume at 1 dose level ↓.
	Fourth	Discontinue.

Dosage with Hepatic Impairment:

Hepatic Impairment	Acalabrutinib Dose
Mild or Moderate (Child-Pugh class A, Child-Pugh class B, or total bilirubin 1.5-3 x ULN with any AST)	No dose adjustment required.
Severe (Child-Pugh class C, or total bilirubin > 3 x ULN with any AST)	Avoid use.

Dosage with Renal Impairment:

Approximate Creatinine Clearance* (mL/min)	Acalabrutinib Dose
≥ 30	No dose adjustment required.
< 30	No data available.

*Reported as eGFR in mL/min/1.73m^2, as estimated by MDRD.

Dosage in the elderly:

No dose adjustment is necessary due to age. Clinically relevant differences in safety or efficacy were not observed between those ≥ 65 years and < 65 years.

Children:

Safety and efficacy in children have not been established.

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F - Administration Guidelines

- Administer acalabrutinib with or without food.
- Tablets or capsules should be swallowed whole with a glass of **water** and not crushed, dissolved, opened, or divided. Acidic beverages (i.e. orange juice or grapefruit juice) decrease absorption of acalabrutinib **capsules**.
- If a dose is missed, patient may take within 3 hours of missed dose. If more than 3 hours, the dose should be skipped and taken at the next planned time. Extra doses should not be taken to make up for missed dose.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during acalabrutinib treatment.
- Store at room temperature, in original bottle, and away from children or pets.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to acalabrutinib or to any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- Avoid in patients with severe hepatic impairment (Child-Pugh C or total bilirubin > 3 times ULN, regardless of AST levels).
- Avoid concomitant use of strong CYP3A4 inhibitors.
- Use caution in patients at risk of bleeding, including those receiving concomitant antiplatelet or anticoagulant medications. Consider the benefits and risks of withholding acalabrutinib for at least 3 days pre-and post-surgery.
- Use caution in patients at risk of cardiac arrhythmias (e.g. history of atrial fibrillation or infection / pneumonia).
- Use caution when driving or operating a vehicle or potentially dangerous machinery due to fatigue and dizziness.

Pregnancy and Lactation:

- Fetotoxicity: Documented in animals
  Acalabrutinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for **2 weeks** after receiving the last dose.
- Fertility effects: Unlikely
  No data on the effect of acalabrutinib on human fertility. No effects on fertility were observed in animals exposed up to 10 times the human AUC at the recommended dose.

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H - Interactions

Acalabrutinib is primarily metabolized by CYP3A enzymes. No interaction is expected with CYP3A substrates.

Acalabrutinib may increase exposure to BCRP substrates (e.g. methotrexate) by intestinal BCRP inhibition; ACP-5862 (active metabolite) may increase exposure to MATE1 substrates by MATE1 inhibition.

Acalabrutinib tablets and capsules are bioequivalent and have equivalent oral bioavailability **except** when given concomitantly with proton pump inhibitors and other acid reducing agents.

Administration of acalabrutinib **capsules** with acidic beverages (i.e. orange juice or grapefruit juice) decreases absorption of acalabrutinib.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ acalabrutinib concentration and/or toxicity	↓ metabolism of acalabrutinib	Avoid. If co-administration with a strong CYP3A inhibitor is short-term, hold acalabrutinib. When co-administered with a moderate CYP3A inhibitor, ↓ dose to 100 mg daily.
Strong CYP3A4 inducers (i.e. phenytoin,	↓ acalabrutinib concentration and/or efficacy	↑ metabolism of acalabrutinib	Avoid.

rifampin, carbamazepine, etc)			
Gastric acid reducing agents (i.e. proton pump inhibitors, H2-receptor antagonists, antacids)	↓ acalabrutinib concentration and/or efficacy	↓ acalabrutinib Capsule absorption	Avoid use of acalabrutinib CAPSULES with proton pump inhibitors. Take acalabrutinib CAPSULES 2 hours before taking a H2-receptor antagonist. Separate dosing by at least 2 hours with antacids. Acalabrutinib TABLETS can be co-administered with gastric acid reducing agents.
Antithrombotic agents	↑ bleeding risk	Unknown	Consider benefits and risks of co-administration

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and at each visit
Renal and liver function tests	Baseline and at each visit
ECG	Baseline and as clinically indicated
Clinical toxicity assessment for cardiac symptoms, skin cancers, infection, hyperuricemia, TLS, GI effects, pain and bleeding	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- acalabrutinib - For the treatment of adult patients with chronic lymphocytic leukemia (CLL), according to clinical criteria

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K - References

Acalabrutinib: DynaMed drug monograph. Dec 06, 2019.

Acalabrutinib: UpToDate® drug information (v48.0). Accessed Jan 30, 2020.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis: Version 1.2019, 2019.

Prescribing information: Calquence (acalabrutinib). AstraZeneca (USA). Nov 2019.

Product Monograph: Calquence (acalabrutinib) capsules. AstraZeneca Canada Inc. Nov 28, 2019.

Product Monograph: Calquence (acalabrutinib) tablets. AstraZeneca Canada Inc. March 2023.

Sharman JP, Banerji V, Fogliatto LM, et al. Elevate TN: Phase 3 study of acalabrutinib combined with obinutuzumab (O) or alone vs O plus chlorambucil (Clb) in patients (Pts) with treatment-naïve chronic lymphocytic leukemia. Blood 2019; 134 (Supplement_1): 31.https://doi.org/10.1182/blood-2019-128404.

July 2024 Updated Dosage with Hepatic Impairment section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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