DRUG NAME: Acalabrutinib

SYNONYM(S): ACP-196[1], acalabrutinib maleate[2]

COMMON TRADE NAME(S): CALQUENCE®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Acalabrutinib is a highly-selective, small-molecule inhibitor of Bruton's tyrosine kinase (BTK). BTK is an integral part of the B-cell antigen receptor (BCR) pathway, which is associated with the pathogenesis of several B-cell malignancies. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions. Acalabrutinib inhibits BTK-mediated activation of downstream signaling proteins and B-cell proliferation and tumour growth, with minimal activity on other immune cells.[3]

PHARMACOKINETICS:

Oral Absorption	bioavailability = 25%; T_{max} = 0.9 h (acalabrutinib) and 1.6 h (ACP-5862); high-fat, high calorie food intake did not affect mean AUC but decreased C_{max} by 80% and delayed T_{max} by 1-2 hours[1,3-5]; acalabrutinib **capsules** and acalabrutinib maleate **tablets** have equivalent oral bioavailability except when administered with acid reducing agents[2]	
Distribution	highly protein bound	
	cross blood brain barrier?	no information found
	volume of distribution	101 L (acalabrutinib); 67 L (ACP-5862)
	plasma protein binding	97.5% (acalabrutinib); 98.6% (ACP-5862)
Metabolism	primarily metabolized by CYP 3A4 enzymes	
	active metabolite(s)	ACP-5862 (major)
	inactive metabolite(s)	no information found
Excretion	primarily fecal excretion (as metabolites)	
	urine	12% (<2% as unchanged drug)
	feces	84% (<2% as unchanged drug)
	terminal half life	1 h (acalabrutinib); 3.5 h (ACP-5862)
	clearance	71 L/h (acalabrutinib); 13 L/h (ACP-5862)
Elderly	no clinically significant difference	

Adapted from standard reference[1,3-5] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic lymphocytic

*Lymphoma, mantle cell

Lymphoma, non-Hodgkin's[4]

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- acalabrutinib **capsules** and acalabrutinib maleate **tablets** have been demonstrated to be bioequivalent except when administered concurrently with acid reducing agents[2]
- ***risk of bleeding*** may be increased with co-administration of anticoagulants or medications that inhibit platelet function; consider withholding treatment for 3-7 days pre- and post- surgery[3,4]
- ***opportunistic infections***, including ***hepatitis B reactivation*** may occur[3]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***.[6]
- ***atrial fibrillation*** and ***atrial flutter*** are reported; risk may be increased in patients with cardiac risk factors, preexisting cardiovascular disease, hypertension, previous history of atrial fibrillation, and infection/pneumonia[3]
- ***drug interactions*** involving the CYP 3A4 metabolism pathway are possible; starting dose adjustment may be required[3]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test or mammalian *in vivo* mutation test. Acalabrutinib is not clastogenic in mammalian *in vitro* chromosome test.

Fertility: In animal studies, no effects on fertility were observed in males or females at exposures higher than those seen following human clinical exposure.[3]

Pregnancy: In animal studies, no maternal toxicity and no evidence of teratogenicity or fetal development, growth or survival was observed at exposures approximately equal to those seen following human clinical exposure. At exposures higher than those seen following human clinical exposure, reduced fetal growth, delayed ossification, underdeveloped renal papilla and dystocia were observed. Women of child-bearing potential should use effective contraception during treatment and for at least one week following the last dose.[3,4]

Breastfeeding is not recommended due to the potential secretion into breast milk. In animal studies, acalabrutinib and its active metabolite were present in milk. Women should not breastfeed during treatment and for two weeks following the last dose.[3,4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia see paragraph following **Side Effects** table	***anemia*** (13-53%, severe 7-15%)
	febrile neutropenia (1-5%)
	lymphocytosis (16-26%, severe 15-19%)
	lymphopenia (severe 7%)
	neutropenia (10-48%, severe 10-23%)
	thrombocytopenia (10-33%, severe 3-7%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	***atrial fibrillation/flutter*** (5%, severe 1%)
eye	blurred vision (5-10%)
	lacrimation increase (5-10%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (8-15%, severe ≤2%)
	constipation (7-15%)
	diarrhea (18-36%, severe 1-3%)
	nausea (7-22%, severe ≤2%)
	stomatitis (5-10%)
	vomiting (12-15%, severe 1-2%)
general disorders and administration site conditions	asthenia (5-17%, severe 1-2%)
	fatigue (10-28%, severe 1-2%)
	peripheral edema (9%, severe 1%)
	pyrexia (7-16%, severe ≤1%)
infections and infestations	bronchitis (5-10%)
	herpesvirus infection (5%)
	infection (56-65%, severe 14-19%)
	lower respiratory tract infection, including pneumonia (10-23% severe 2-6%)
	nasopharyngitis (5-10%)
	sinusitis (12%)
	upper respiratory tract infection (10-35%, severe 2%)
	urinary tract infection (12-15%, severe 2-3%)
injury, poisoning, and procedural complications	falls (5-10%)
investigations	***ALT increase*** (15-20%, severe 1-2%)
	AST increase (13-17%, severe 1%)
	bilirubin increase (13-15%, severe 1%)
	uric acid increase (15-22%, severe 15-22%)
metabolism and nutrition	appetite decrease (5-10%)
	tumour lysis syndrome (severe 1%)
musculoskeletal and connective tissue	arthralgia (8-16%, severe 1%)
	back pain (5-10%)
	muscle spasms (5-10%)
	musculoskeletal pain (15-32%, severe 1%)
	myalgia (21%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pain in extremity (5-10%)
neoplasms	***second primary malignancy*** (8-12%, severe 1-4%); see paragraph following **Side Effects** table
nervous system	dizziness (6-12%)
	headache (22-39%, severe 1-2%)
	memory impairment (5-10%)
	paraesthesia (5-10%)
psychiatric	insomnia (5-10%)
respiratory, thoracic and mediastinal	cough (22%)
	dyspnea (10%, severe 2%)
	epistaxis (6%)
skin and subcutaneous tissue	***bruising*** (10-26%)
	erythema (5-10%)
	rash (7-25%, severe 1-2%)
vascular	***hemorrhage/hematoma*** (8-22%, severe 1-3%)
	hypertension (3%)
	hypotension (5-10%)

Adapted from standard reference[1,3,4] unless specified otherwise.

Hematologic toxicities, including grade 3 or 4 neutropenia, anemia, thrombocytopenia, and febrile neutropenia, are reported. Upon treatment initiation, a temporary increase in lymphocyte count may occur; median onset of lymphocytosis is 1 week and median duration is 7 weeks. Treatment interruption, dose reduction, or treatment discontinuation may be required for hematologic toxicity.[3,4]

Second primary malignancies, including skin or other solid tumours, have been reported. Skin cancer was the most frequent second primary malignancy and was reported in 6% of patients. Monitor for the appearance of skin cancers and advise patients on appropriate sun protection measures.[3,4]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
calcium carbonate[3,4]; other antacids	53% decrease in AUC of acalabrutinib (**capsule** formulation)[3]; no pharmacokinetic differences are reported with acalabrutinib maleate **tablets**[2]	reduced solubility of acalabrutinib **capsules** with increasing pH[3] (NOTE: pH effect is not seen with acalabrutinib maleate **tablets**)[2]	separate administration of antacid from acalabrutinb **capsules** by at least 2 hours[3] (NOTE: spacing of antacid is not required if using acalabrutinib maleate **tablets**)[2]

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AGENT	EFFECT	MECHANISM	MANAGEMENT
diltiazem[3,4]	*predicted* 2- to 3-fold increase in C_{max} and AUC of acalabrutinib	moderate CYP 3A4 inhibition by diltiazem	if concurrent use cannot be avoided, reduce acalabrutinib dose to 100 mg PO once daily
erythromycin[3,4]	*predicted* 2- to 3-fold increase in C_{max} and AUC of acalabrutinib	moderate CYP 3A4 inhibition by erythromycin	if concurrent use cannot be avoided, reduce acalabrutinib dose to 100 mg PO once daily
fluconazole[3,4]	*predicted* 2- to 3-fold increase in C_{max} and AUC of acalabrutinib	moderate CYP 3A4 inhibition by fluconazole	if concurrent use cannot be avoided, reduce acalabrutinib dose to 100 mg PO once daily
grapefruit juice[2,3]	17% **decrease** in AUC of acalabrutinib when **capsule** formulation is administered with grapefruit juice vs water[3] grapefruit juice may **increase** acalabrutinib plasma levels by CYP 3A4 inhibition[2,10]	pH dependent solubility of acalabrutinib **capsules**[3]; (NOTE: pH effect is not seen with acalabrutinib maleate **tablets**)[2] AND grapefruit juice may inhibit CYP 3A4 metabolism of acalabrutinib in the intestinal wall[2,10]	avoid taking acalabrutinib **capsules** with grapefruit juice; administration with water is preferred[3] avoid grapefruit and grapefruit juice during treatment with acalabrutinib **capsules**[10] and acalabrutinib maleate **tablets**[11]
H_2-blockers[3,4]	*predicted* decrease in AUC of acalabrutinib (**capsule** formulation)[3]; no pharmacokinetic differences are reported with acalabrutinib maleate **tablets**[2]	reduced solubility of acalabrutinib **capsules** with increasing pH[3]; (NOTE: pH effect is not seen with acalabrutinib maleate **tablets**)[2]	administer acalabrutinib **capsules** 2 hours prior to the H_2-blocker[3] (NOTE: spacing of H_2-blocker is not required if using acalabrutinib maleate **tablets**)[2]
itraconazole[3,4]	3.7-fold increase in C_{max} and 5.1-fold increase in AUC of acalabrutinib	strong CYP 3A4 inhibition by itraconazole	avoid concurrent use; if unavoidable, acalabrutinib may be held for short-term use of itraconazole (i.e., ≤7 days)
omeprazole[3,4], rabeprazole[2], other proton pump inhibitors	43% decrease in AUC of acalabrutinib (**capsule** formulation)[3]; no pharmacokinetic differences are reported with acalabrutinib maleate **tablets**[2]	reduced solubility of acalabrutinib **capsules** with increasing pH[3]; (NOTE: pH effect is not seen with acalabrutinib maleate **tablets)**[2]	avoid concurrent use of PPIs with acalabrutinib **capsules**[3]; consider using an H_2-blocker instead[3] (NOTE: acalabrutinib maleate **tablets** can be taken with proton pump inhibitors)[2]

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AGENT	EFFECT	MECHANISM	MANAGEMENT
orange juice, other acidic beverages[3]	40% decrease in AUC of acalabrutinib when **capsule** formulation is administered with orange juice[3]; no data is available for acalabrutinib maleate **tablets**	pH dependent solubility of acalabrutinib **capsules**[3]; (NOTE: pH effect is not seen with acalabrutinib maleate **tablets**)[2]	avoid taking acalabrutinib **capsules** with orange juice and other acidic beverages; administration with water is preferred[3]; (NOTE: no action required for acalabrutinib maleate **tablets**)
rifampin[3,4]	68% decrease in C_{max} and 77% decrease in AUC of acalabrutinib	strong CYP 3A4 induction by rifampin	avoid concurrent use; if unavoidable, consider increasing acalabrutinib dose to 200 mg PO BID[4]

Acalabrutinib is a substrate of ***CYP 3A4***. ***CYP 3A4 inhibitors*** may increase the plasma concentration of acalabrutinib. Dose adjustment is not required for concurrent use with *weak* CYP 3A4 inhibitors; monitor for adverse reactions. Avoid concurrent use with *moderate or strong* CYP 3A4 inhibitors if possible. For coadministration with a *moderate* inhibitor, reduce acalabrutinib dose to 100 mg PO once daily. If coadministration with a *strong* inhibitor is unavoidable but expected to be short-term (≤7 days), acalabrutinib may be temporarily withheld to avoid the interaction. ***CYP 3A4 inducers*** may decrease the plasma concentration of acalabrutinib. Avoid concurrent use with *strong* CYP 3A4 inducers. If coadministration is unavoidable, consider increasing acalabrutinib dose to 200 mg PO BID.[3,4]

Acalabrutinib is an *inhibitor* of intestinal BCRP *in vitro* and may increase exposure to coadministered BCRP substrates; clinical significance is unknown.[3,4]

ACP-5862 is an *inhibitor* of MATE1 and may increase exposure to coadministered MATE1 substrates; clinical significance is unknown.[3,4]

In vitro, acalabrutinib is an *inhibitor* of CYP 3A4/5, CYP 2C8, and CYP 2C9, and an *inducer* of CYP 1A2, CYP 2B6, and CYP 3A4. *In vitro*, ACP-5862 is an inhibitor of CYP 2C8, CYP 2C9, and CYP 2C19, and an inducer of CYP 3A4. *In vitro, a*calabrutinib and ACP-5862 are also *substrates* of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Clinical significance is unknown.[3,4]

SUPPLY AND STORAGE:

Oral:
AstraZeneca Canada Inc. supplies acalabrutinib as 100 mg hard gelatin **capsules**. Capsules contain propylene glycol. Store at room temperature.[3]

AstraZeneca Canada Inc. supplies acalabrutinib maleate as 100 mg **tablets**. Store at room temperature.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:[3,4,12,13]

100 mg PO twice daily*

Administer doses approximately 12 hours apart. Administer with food or on an empty stomach.

*starting dose adjustment may be required for some drug interactions

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: creatinine clearance ≥ 30 mL/min: no adjustment required[3,4]
creatinine clearance < 30 mL/min: no information found

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

Child-Pugh Classification	Total Bilirubin	AST	Dosage recommendation
class A or B	1.5-3 x ULN	any	no adjustment required
class C	>3 x ULN	any	avoid [3,4]

Dosage in dialysis: no information found

Children: safety and efficacy have not been established

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