DRUG NAME: Asciminib

SYNONYM(S): ABL001[1], asciminib hydrochloride[2]

COMMON TRADE NAME(S): SCEMBLIX®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Asciminib is an orally administered allosteric BCR-ABL1 inhibitor, specifically targeting the ABL myristoyl pocket (STAMP). This binding site is normally occupied by the myristoylated N-terminal of ABL1 for autoinhibition. On fusion of ABL1 to BCR, the myristoylated N-terminal is lost and locks the ABL1 kinase in the active state. Asciminib binds to the vacant pocket and blocks kinase activity, preventing tumour cell proliferation. Asciminib demonstrates activity against both wild-type and mutated BCR-ABL1, including the T315I mutation.[1-4]

PHARMACOKINETICS:

Oral Absorption	Tmax = 2.5 h; AUC is decreased following both high fat meals (by 62%) and low fat meals (by 30%)	
Distribution	blood to plasma concentration ratio = 0.58	
	cross blood brain barrier?	no information found
	volume of distribution	111-151 L
	plasma protein binding	97%
Metabolism	primarily metabolized by CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily eliminated via fecal excretion	
	urine	11% (2.5% as unchanged drug)
	feces	80% (57% as unchanged drug)
	terminal half life	5.5-15 h
	clearance	4-6 L/h

Adapted from standard reference[2,3] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic myelogenous

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:

- ***fatal arterial thromboembolism*** and ***ischemic stroke*** have occurred in patients with pre-existing cardiovascular conditions and prior exposure to tyrosine kinase inhibitors (TKIs)[2,5]
- ***QTc prolongation*** and ***arrhythmia*** have been reported; monitor ECG and electrolytes in patients with known risk factors and correct electrolyte abnormalities prior to treatment[2,6]
- patients reporting ***pancreatitis*** with a previous TKI may be at increased risk of experiencing pancreatitis with asciminib[1]
- ***reactivation of Hepatitis B virus (HBV)*** has occurred in chronic carriers of HBV after receiving TKIs[2]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***.[7]

Carcinogenicity: No carcinogenicity studies have been conducted.[6]

Mutagenicity: Not mutagenic in Ames test. Asciminib was not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.[6]

Fertility: In animal studies, asciminib did not affect reproductive function in male or female test subjects and there were no effects on fertility indices or conception rates. However, the mean number of live embryos was decreased (attributed to fewer implantations and increased early resorptions in study subjects) and a slight reduction in sperm motility and sperm count was observed at exposures higher than those seen following human clinical exposure.[2]

Pregnancy: Animal studies demonstrated that administration of asciminib during organogenesis induced embryotoxicity, fetotoxicity, and teratogenicity at exposures similar to the expected human systemic exposure following clinically recommended doses. Observed effects included increased post-implantation losses and structural malformations, and reduced numbers of viable fetuses. Contraception is recommended during treatment and for at least 1 week after the last dose for female patients of reproductive potential and male patients with female partners of reproductive potential.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk. Breastfeeding should be avoided during treatment and for at least 1 week after the last dose.[2]

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.[8,9]

Incidence range in the *Side Effects* table is from pooled safety data and reflects asciminib exposure at doses up to 200 mg twice daily.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (13%, severe 5%)
	febrile neutropenia (1%)
	lymphocytopenia (18-42%, severe 3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neutropenia (19%, severe 16%)
	thrombocytopenia (28%, severe 19%)
cardiac	arrhythmia (7%, severe 2%)
	cardiovascular toxicity (8-13%, severe 4%)
	heart failure (3-8%, severe 1-2%)
	palpitations (3%)
eye	blurred vision (3%)
	dry eye (2%)
gastrointestinal	*emetogenic potential*: low[10]
	abdominal pain (10-17%, severe 1-8%)
	constipation (5%)[5]
	diarrhea (12-21%, severe 2%)
	dyspepsia (5%)[5]
	nausea (12-27%, severe 1%)
	pancreatitis (3%, severe 1%); see paragraph following **side effects** table
	vomiting (7-19%, severe 1-6%)
general disorders and administration site conditions	***asthenia/fatigue*** (17-31%, severe 2%)
	peripheral edema (6-10%, severe 4%)
	pyrexia (4%, severe 1%)[5]
immune system	***hypersensitivity*** (32%, severe 2%); see paragraph following **side effects** table
infections and infestations	influenza (3%)
	lower respiratory tract infection (4%)
	pneumonia (4%)[6]
	upper respiratory tract infection (13-26%, severe 1%); includes nasopharyngitis, rhinitis, and pharyngitis
	urinary tract infection (5%, severe 1%)[1]
investigations	alkaline phosphatase increase (13%)
	ALT increase (23-48%, severe 1-6%)
	amylase increase (12-29%, severe 1-10%)
	AST increase (19-35%, severe 1-2%)
	bilirubin increase (12-23%)
	calcium corrected decrease (14-33%, severe 1%)
	cholesterol increase (11-15%)
	creatine kinase increase (27-31%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	creatinine increase (14-31%)
	hemoglobin decrease (35-44%, severe 2-4%)
	lipase increase (14-46%, severe 4-21%)
	phosphate decrease (17-40%, severe 6%)
	potassium decrease (10-48%, severe 2%)
	QTc prolongation (1%, severe <1%)
	triglycerides increase (44%, severe 2-5%)
	uric acid increase (19-40%, severe 4-6%)
metabolism and nutrition	appetite decrease (5%)
musculoskeletal and connective tissue	arthralgia (12-17%)
	musculoskeletal pain (22-42%, severe 1-4%); includes myalgia, back, neck, limb, bone, and non-cardiac chest pain
nervous system	dizziness (7%)
	headache (19-24%, severe 2%)
	ischemic stroke (severe <1%)
psychiatric	insomnia (5%)[5]
respiratory, thoracic and mediastinal	cough (7-15%)
	dyspnea (5%, severe 1-6%)
	pleural effusion (1-3%)
skin and subcutaneous tissue	dry skin (2%)
	pruritus (5-13%)
	rash (7-27%)
	urticaria (1%)
vascular	arterial thromboembolism (severe <1%)
	hemorrhage (15%, severe 2%);[2,3,6] see paragraph following **side effects** table
	hypertension (13-19%, severe 6-8%)

Adapted from standard reference[2,6] unless specified otherwise.

Pancreatitis has been reported in 3% of patients. The majority of these patients had experienced pancreatitis with previous TKI therapy prior to treatment with asciminib. Higher asciminib doses (e.g., total daily dose of 160 mg or more) were associated with higher rates of clinical pancreatitis.[1] Dose interruption or reduction may be required for asymptomatic elevation of pancreatic enzymes. If lipase and amylase elevations occur with abdominal symptoms, hold asciminib until pancreatitis diagnosis has been ruled out.[2,6]

Hemorrhagic events have been reported in patients receiving higher doses of asciminib (e.g., 200 mg twice daily).[3,6] Reported events include epistaxis, post procedural hemorrhage, and hemorrhage at various sites such as

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upper gastrointestinal, ear, skin, and vagina.[1,6] Withhold asciminib for grade 3 or 4 events and consider permanent discontinuation if symptoms persist.[2,6]

Hypersensitivity has been reported in 32% of patients, although grade 3 or 4 reactions are uncommon. Reactions include rash, edema, and bronchospasm. Withhold asciminib until symptom recovery to grade 1 or less. Asciminib may be resumed at a reduced dose if the hypersensitivity event has resolved.[2,6]

INTERACTIONS:

The effect reported in the table below is based on asciminib doses of 40 mg or 80 mg daily unless otherwise indicated. When using higher doses of asciminib (e.g., 200 mg twice daily), the magnitude of the effect of the interaction is expected to be greater.

AGENT	EFFECT	MECHANISM	MANAGEMENT
clarithromycin[2]	36% increase in AUC and 20% increase in Cmax of asciminib	strong inhibition of CYP 3A4 by clarithromycin	no dose adjustment required as not considered clinically meaningful
imatinib[2,6]	108% increase in AUC and 59% increase in Cmax of asciminib	combined inhibition of CYP 3A4, BCRP, and UGT2B17 by imatinib	no dose adjustment required as not considered clinically meaningful; monitor for toxicity of asciminib
itraconazole[2]	no clinically meaningful effect on AUC or Cmax of asciminib[6]	strong inhibition of CYP 3A4 by itraconazole	itraconazole **capsule:** no dose adjustment required; itraconazole **oral solution:** see hydroxypropyl-β-cyclodextrin
hydroxypropyl-β-cyclodextrin (used as excipient e.g., itraconazole oral solution)[2]	40% decrease in AUC and 50% decrease in Cmax of asciminib; may reduce efficacy of asciminib	decreased absorption of asciminib due to hydroxypropyl-β-cyclodextrin binding of asciminib	avoid concurrent use; consider using alternate formulation (e.g., suggest capsule formulation of itraconazole)
midazolam[6]	24% increase in AUC and 17% increase in Cmax of midazolam (greater effect observed with asciminib at 200 mg twice daily: 88% increase in AUC and 58% increase in Cmax of midazolam)	inhibition of CYP 3A4 by asciminib	monitor for toxicity of midazolam
rabeprazole[2]	no effect on AUC or Cmax of asciminib	increase in gastric pH by rabeprazole	no dose adjustment required
repaglinide[6]	12% increase in AUC and 8% increase in Cmax of repaglinide (greater effect observed with asciminib at 200 mg twice daily: 42% increase in AUC and 25% increase in Cmax of repaglinide)	inhibition of CYP 2C8 by asciminib	monitor for hypoglycemia and adjust repaglinide treatment as clinically appropriate

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AGENT	EFFECT	MECHANISM	MANAGEMENT
rifampicin[2]	14.9% decrease in AUC and 9% increase in Cmax of asciminib	strong induction of CYP 3A4 by rifampicin	clinical significance is unknown
warfarin[6]	52% increase in AUC and 8% increase in Cmax of warfarin (greater effect observed with asciminib at 200 mg twice daily: 314% increase in AUC and 7% increase in Cmax of warfarin)	inhibition of CYP 2C9 by asciminib	monitor INR and adjust warfarin dose as needed; recommend increased frequency of monitoring with higher doses of asciminib

Asciminib is a substrate of ***CYP 3A4.*** At asciminib doses of 80 mg daily, the effect of concurrent administration with ***CYP 3A4 inhibitors*** is not expected to be clinically significant.[2] When using higher doses (e.g., 200 mg twice daily), the clinical significance of concurrent administration with CYP inhibitors is unknown. However, it is expected that the magnitude of the effect on asciminib plasma concentrations will be greater, particularly if ***strong CYP 3A4 inhibitors*** are used. Monitor for asciminib toxicity. Clinical significance of concurrent administration with ***CYP 3A4 inducers*** is unknown; however, ***strong CYP 3A4 inducers*** may decrease the plasma concentration of asciminib and reduce its efficacy.[2,6]

Asciminib is an inhibitor of P-glycoprotein (P-gp), CYP 2C9, and CYP 2C8. Concomitant administration with a P-gp substrate or a substrate of these enzymes may increase the plasma concentration of the substrate; monitor for toxicity of the substrate.[2,6]

In vitro, asciminib is an inhibitor of CYP 2C19, and a substrate of P-gp and BCRP; clinical significance is unknown.[2,6]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies asciminib as 20 mg and 40 mg film-coated tablets. Store at room temperature. Keep in original packaging to protect from moisture. Tablets contain lactose.[2]

Additional information: Asciminib tablets are packaged in blister cards containing 10 blisters per card. Each carton contains 6 blister cards. When dispensing for dose modifications, blister cards may be cut to separate individual blisters from the card, as long as the blisters themselves are not compromised.[11]

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.

Adults:

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

Oral: ***40 mg*** (range 20-40 mg) ***PO twice daily***[2,12]
Administer on an empty stomach (at least 1 hour before meals or 2 hours after) at times approximately 12 hours apart.

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

80 mg (range 40-80 mg) PO once daily[2]
Administer on an empty stomach (at least 1 hour before meals or 2 hours after) at approximately the same time each day.

200 mg (range 160-200 mg) PO twice daily[2,6]
Administer on an empty stomach (at least 1 hour before meals or 2 hours after) at times approximately 12 hours apart.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, the following adjustments may be used:

	Dose[2,6]	
Starting dose	40 mg twice daily (or 80 mg once daily)	200 mg twice daily
First dose reduction	20 mg twice daily (or 40 mg once daily)	160 mg twice daily
Subsequent dose reduction	Discontinue if unable to tolerate first dose reduction	

ANC ($x10^9$/L)		**Platelet** ($x10^9$/L)	**Management**[2,6]
≥1.0	and	≥50	no dose adjustment
<1.0	or	<50	hold until recovery of blood counts[†] • recovery **within 2 weeks**: resume at starting dose (refer to table above) • recovery **after 2 weeks**: restart at reduced dose (refer to table above)

[†]for **recurrent severe** neutropenia/thrombocytopenia: restart at reduced dose

Dosage in renal failure: eGFR ≥15 mL/min/1.73 m^2 not requiring dialysis: no adjustment required[2,3,6]

Dosage in hepatic failure: no adjustment required[2,3]

Dosage in dialysis: no information found

Children: safety and efficacy have not been established[2]

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