

DRUG NAME: Nilotinib**SYNONYM(S):** nilotinib hydrochloride monohydrate¹**COMMON TRADE NAME(S):** TASIGNA®**CLASSIFICATION:** miscellaneous*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Nilotinib is a potent inhibitor of Abl tyrosine kinase activity of the Bcr-Abl oncoprotein.¹ This leads to selective inhibition of proliferation and induction of apoptosis.¹ It binds with high affinity to the ATP-binding site in such a manner that it inhibits wild-type Bcr-Abl and maintains activity against 32 of 33 imatinib-resistant forms of Bcr-Abl (T315I mutant excepted).^{1,2} Other targets include c-Kit and platelet derived growth factor receptor (PDGFR).³ Nilotinib is cell cycle phase-nonspecific.¹ Nilotinib is an immunosuppressive agent.¹

PHARMACOKINETICS:

Oral Absorption	30%; pH-dependent solubility ⁴ ; increased when taken with food ¹⁻³ ; AUC increased 82% when administered 30 minutes after a high-fat meal ¹⁻³	
Distribution	time to peak ^{1,3} : 3-4 h	
	cross blood brain barrier?	no information found
	volume of distribution	579 L
	plasma protein binding ^{1,3}	98%
Metabolism	mainly hepatic; oxidation and hydroxylation, via cytochrome P450, primarily CYP 3A4 ¹⁻³	
	active metabolite(s)	none substantially contribute to activity ¹⁻³
	inactive metabolite(s)	yes ^{2,3}
Excretion	non-renal; including P-glycoprotein	
	urine	none
	feces ¹⁻³	93%; 69% as unchanged drug
	terminal half life ^{1,3}	15-17 h
	clearance	29 L/h

Adapted from standard reference¹ unless specified otherwise.**USES:****Primary uses:**

*Leukemia, chronic myelogenous

*Health Canada approved indication

Other uses:Leukemia, acute lymphoblastic³**SPECIAL PRECAUTIONS:****Contraindications:**

- long QT syndrome¹⁻³
- hypokalemia or hypomagnesemia¹⁻³

Caution:

- **baseline ECG** is recommended and should be repeated seven days after start of treatment and as clinically indicated, including seven days after dose changes^{1,2}
- avoid use in patients who are at risk for developing **prolonged QT interval** whether due to an underlying medical condition, concurrent anti-arrhythmic medications or other drugs that may lead to QT prolongation, or those who have received cumulative high-dose anthracycline therapy¹
- concurrent medications should be reviewed carefully for **potential interactions**, particularly in regard to CYP 3A4, 2B6, 2C8, 2C9, 2D6, UGT1A1, and P-glycoprotein
- caution in patients with uncontrolled or significant **cardiac disease** including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia¹
- hypokalemia, hypomagnesemia, and other **electrolyte abnormalities** must be corrected prior to beginning treatment and levels should be monitored periodically^{1,2}
- CBC should be done every one to two weeks for the first two months and then monthly, due to risk for **thrombocytopenia, neutropenia, and anemia**^{1,2,5}
- liver function and serum lipase should be monitored periodically during treatment, especially in those with a history of **pancreatitis**^{1,2}
- **reactivation of Hepatitis B virus (HBV)** has sometimes occurred in chronic carriers of HBV after receiving BCR-ABL tyrosine kinase inhibitors; test for HBV infection prior to treatment and monitor for signs of active HBV infection.⁶

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* mutation tests.¹ Unknown if clastogenic.

Fertility: No effects noted in rat studies.¹

Pregnancy: FDA Pregnancy Category D.³ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Spontaneous abortions, premature delivery, fetal abnormalities, and fetal deaths have been reported by women taking nilotinib during pregnancy. It is not known if nilotinib is present in semen, however spontaneous abortions, premature delivery, and fetal abnormalities have been reported by the female partners of male patients taking nilotinib. Effective contraception is recommended during treatment and for at least four weeks after treatment in females of child-bearing potential and in male patients whose partners are females of child-bearing potential.^{7,8}

Breastfeeding is not recommended due to the potential secretion into breast milk.¹⁻³

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.^{9,10}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow/ febrile neutropenia	<i>anemia</i> (13%, severe 8-23%) ¹⁻³ ; generally reversible
	febrile neutropenia (1-5%)
	<i>neutropenia</i> (15%, severe 28-37%) ¹⁻³ ; generally reversible; median duration 15 days ³ ; see paragraph following Side Effects table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	<p>thrombocytopenia (27%, severe 7-30%)^{1,3}; generally reversible; median duration 22 days³; see paragraph following Side Effects table</p> <p>pancytopenia (1-5%)</p>
cardiovascular (arrhythmia)	cardiac flutter
	extrasystoles
	palpitations (1-5%)
	QT interval prolongation (1-5%); see paragraph following Side Effects table
cardiovascular (general)	atherosclerotic-related diseases (2-6%) ¹¹ ; including peripheral arterial occlusive disease; femoral, coronary, or carotid artery stenosis; cerebrovascular accident
	congestive heart failure (1%)
	hypertension (1-5%)
	myocardial infarction
	pericardial effusion (1%)
	pericarditis
	ventricular dysfunction
constitutional symptoms	asthenia (6-14%) ^{1,3}
	fatigue (16-28%) ^{1,3}
	pyrexia (1-24%) ^{1,3}
	weight decreased (1-5%)
	weight increased (1-5%)
dermatology/skin	alopecia (7%)
	dry skin (1-5%)
	eczema (1-5%)
	erythema (1-5%)
	flushing (1-5%)
	hyperhidrosis (1-5%)
	night sweats (1-5%)
	pruritis (20-29%) ^{1,3}
	rash (26-33%) ^{1,3}
	urticaria (1-5%)
endocrine	hyperglycemia (severe 4-11%) ^{1,3}
gastrointestinal	<i>emetogenic potential: low</i> ¹²
	abdominal discomfort (1-5%)
	anorexia (5%)
	constipation (11-21%) ^{1,3}
	diarrhea (10-22%) ^{1,3}
	dyspepsia (1-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	flatulence (1-5%)
	nausea (18-31%) ^{1,3}
	vomiting (9-21%) ^{1,3}
hemorrhage	CNS hemorrhage (1%)
	gastrointestinal hemorrhage (3%)
hepatobiliary/pancreas	hepatotoxicity , as evidenced by elevated alkaline phosphatase, ALT, AST, and bilirubin
	pancreatitis (1%)
lymphatics	peripheral edema (5-11%) ^{1,3}
metabolic/laboratory	albumin decreased (severe 1%)
	alkaline phosphatase increased (1-5%, severe 1-3%) ^{1,3}
	ALT increased (1-5%; severe 2-4%) ^{1,3}
	amylase increased (1-5%); see paragraph following Side Effects table
	AST increased (1-5%, severe 1%) ^{1,3}
	bilirubin increased (severe 9-10%) ^{1,3} ; the largest increases were observed in patients with UGT1A1*28 polymorphism ²
	blood glucose increased (1-5%)
	creatine phosphokinase increased (1-5%)
	gamma-glutamyltransferase increased (1-5%)
	hyperkalemia (severe 3-4%) ^{1,3}
	hypocalcemia (severe 1-4%) ^{1,3}
	hypokalemia (severe 1-5%) ^{1,3}
	hypomagnesemia (1-5%)
	hyponatremia (severe 3%)
	hypophosphatemia (severe 10%)
	lipase increased (>10%, severe 15-17%) ¹⁻³ ; see paragraph following Side Effects table
musculoskeletal	arthralgia (6-18%) ^{1,3}
	muscle spasm (6-14%) ^{1,3}
	myalgia (8-14%) ^{1,3}
neurology	dizziness (1-5%)
	insomnia (1-5%)
	paresthesia (1-5%)
	vertigo (1-5%)
pain	abdominal (5-13%) ^{1,3}
	back (10-12%) ³
	bone (6-13%) ^{1,3}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	headache (15-31%) ^{1,3}
	limb (13-16%) ³
	musculoskeletal (1-5%)
	musculoskeletal, chest (1-5%)
pulmonary	cough (1-17%) ^{1,3}
	dyspnea (1-11%) ^{1,3}
	dyspnea on exertion (1-5%)
	dysphonia (1-5%)
	nasopharyngitis (11-16%) ³
	pleural effusion (1%)

Adapted from standard reference¹ unless specified otherwise.

QT interval prolongation may occur, which may in turn result in torsades de pointes, leading to syncope, seizure, and/or death.¹⁻³ **Sudden deaths** have been reported (0.1-1%); ventricular repolarization abnormalities may have contributed.^{1,2} Prolongation is concentration-dependent.² Significant prolongation may occur if taken inappropriately with food, and/or strong CYP3A4 inhibitors, and/or medicines with a known potential to prolong QT interval.¹ The presence of hypokalemia and hypomagnesemia may further enhance this effect.¹

If the QT interval corrected for rate (QT_c) exceeds 480 msec, nilotinib should be withheld.^{2,3}

- If, within two weeks, the QT_c returns to less than 450 msec and to within 20 msec of baseline, nilotinib may be resumed at the prior dosage.^{2,3}
- If, after two weeks, the QT_c is between 450 and 480 msec, nilotinib may be resumed at a reduced dose of 400 mg once daily.^{2,3}
- If QT_c exceeds 480 msec after this dose reduction, nilotinib should be discontinued.^{2,3}

Neutropenia and/or thrombocytopenia that is not related to the underlying CML may necessitate treatment interruption or dosage reduction.² Complete blood counts should be monitored every one to two weeks during the first two months of therapy and at least monthly thereafter.^{1,2,5} Hold nilotinib if ANC less than 1 x 10⁹ and/or platelets less than 50 x 10⁹.² If ANC and/or platelets rise above these values within two weeks, then treatment may be resumed at the prior dose; if counts remain low for more than two weeks, dose should be reduced to 400 mg once daily.²

Amylase or lipase increases greater than or equal to two times the upper limit of normal (ULN), i.e., NCI CTCAE Grade 3 or 4, require interruption in therapy.³ Resume treatment at reduced dose of 400 mg once daily when level returns to less than or equal to 1.5 times the ULN, i.e., Grade 1.³

Hepatitis B virus (HBV) reactivation has been reported in chronic HBV carriers and patients with a documented history of hepatitis B after receiving BCR-ABL inhibitors. Increased viral load or positive serology may occur with HBV reactivation. Some cases have included acute hepatic failure or fulminant hepatitis leading to liver transplantation or death. The mechanism and frequency of HBV reactivation is not known but may occur at any time during treatment, and is considered a class effect of the BCR-ABL TKIs. Test for HBV infection prior to treatment and monitor for symptoms of active HBV infection during treatment and for several months after termination of treatment.⁶

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antacid (aluminum hydroxide/ magnesium hydroxide/ simethicone) ^{4,13}	may decrease nilotinib absorption	pH-dependent solubility (reduced nilotinib solubility with increased pH)	administer antacid 2 h before or 2 h after nilotinib ^{4,13}
esomeprazole ^{4,14,15}	decreased nilotinib absorption (AUC reduced 34%, C _{max} reduced 27%); no change in half life ^{4,14}	pH-dependent solubility (reduced nilotinib solubility with increased pH)	proton pump inhibitors may be used concurrently with nilotinib as needed ^{4,15}
famotidine ^{4,13,15}	may decrease nilotinib absorption	pH-dependent solubility (reduced nilotinib solubility with increased pH)	administer famotidine or other H ₂ blocker 10 h before or 2 h after nilotinib ^{4,13}
grapefruit juice ^{1,2,16}	may increase nilotinib plasma level	may inhibit CYP 3A4 metabolism of nilotinib in the intestinal wall	avoid grapefruit and grapefruit juice
ketoconazole ^{1,2}	three-fold increase in nilotinib AUC	CYP 3A4 inhibition	avoid ketoconazole or consider reducing nilotinib dose
midazolam ^{1,2}	midazolam exposure increased by 30% (single dose)	CYP 3A4 inhibition by nilotinib	anticipate increased effect; consider dose adjustment
rifampin ²	80% decrease in nilotinib AUC	CYP 3A4 induction	avoid rifampin or consider increasing nilotinib dose, with close monitoring of QT interval
warfarin ²	decreased metabolism of warfarin	inhibition of CYP 3A4 and CYP 2C9 by nilotinib	concomitant use of warfarin should be avoided if possible

Drugs that prolong QT interval should be avoided due to the risk of potentially fatal arrhythmias.¹⁻³

Absorption and elimination of nilotinib may be influenced by drugs that affect CYP 3A4 and/or P-glycoprotein, as nilotinib is a CYP 3A4 and P-glycoprotein substrate.¹⁻³

CYP 3A4 inducers may reduce exposure to nilotinib; increase of nilotinib dose should be considered.^{1,2}

CYP 3A4 inhibitors should be avoided as increased plasma levels of nilotinib may result.^{1,2} Dose adjustment to 400 mg once daily or interruption of nilotinib therapy have been recommended if concurrent use cannot be avoided.^{2,3}

Nilotinib inhibits CYP 3A4, 2C8, 2C9, 2D6, UGT1A1, and P-glycoprotein.^{2,3}

Nilotinib induces CYP 2B6, 2C8, 2C9.^{2,3}

SUPPLY AND STORAGE:

Oral: Novartis supplies nilotinib as 150 mg and 200 mg capsules, containing lactose. Store at room temperature, in original packaging.¹⁷

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:

BCCA usual dose noted in ***bold, italics***

Oral^{1,2,5}:

400 mg PO twice daily.

Administer on an empty stomach (at least one hour before, or two hours after any food); do not take with food.¹⁻³

Swallow whole with water.¹⁻³ Take doses approximately 12 hours apart.^{2,3}

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 6 "Dosage Modification for Myelosuppression"

The following adjustments have been recommended³:

ANC		Platelets	Recommendations
If at any time:			
less than 1 x 10 ⁹ /L	and/or	less than 50 x 10 ⁹ /L	hold treatment; monitor counts
Then, if within two weeks:			
greater than 1 x 10 ⁹ /L	and	platelets greater than 50 x 10 ⁹ /L	continue at 400 mg twice daily
If after two weeks:			
less than 1 x 10 ⁹ /L	and/or	less than 50 x 10 ⁹ /L	reduce dose to 400 mg once daily

Dosage in renal failure:

Dose adjustment likely not required.^{1,2}

Dosage in hepatic failure:

Metabolism is mainly hepatic; increased exposure can be expected in patients with hepatic impairment.^{1,2} Hold treatment if lipase or amylase reach greater than two times the upper limit of normal (ULN), bilirubin greater than 3 x ULN, and/or hepatic transaminase concentrations greater than 5 x ULN (i.e., NCI CTCAE Grade 3 or higher); resume treatment at 400 mg once daily if the toxicity drops to Grade 1 or less (i.e., less than 1.5 x ULN for amylase, bilirubin, and lipase; less than 2.5 x ULN for transaminases).^{2,3}

Dosage in dialysis:

no information found

Children:

Oral:

No clinical studies conducted in children and adolescents.¹ Safety and efficacy not established.³

REFERENCES:

1. Novartis Pharmaceuticals Canada Inc. TASIGNA® product monograph. Dorval, Quebec; 5 September 2009.
2. McEvoy GK, editor. AHFS 2009 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1185-1188.
3. Rose BD editor. Nilotinib. UpToDate 17.1 ed. Waltham, Massachusetts: UpToDate®; 2009.
4. Novartis Pharmaceuticals Canada Inc. TASIGNA® product monograph. Dorval, Quebec; 14 June 2013.
5. BC Cancer Agency Leukemia Tumour Group. (ULKCMLN) BCCA Protocol Summary for Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using Nilotinib. Vancouver, British Columbia: BC Cancer Agency; 1 June 2009.

6. Health Canada. Important Safety Information: BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC® (imatinib mesylate), TASIGNA® (nilotinib), BOSULIF® (bosutinib), SPRYCEL® (dasatinib), ICLUSIG® (ponatinib hydrochloride)] - Risk of Hepatitis B Reactivation. 4 May 2016. Available at: <http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/>.
7. Novartis Pharmaceuticals Canada Inc. TASIGNA® product monograph. Dorval, Quebec; 13 October 2015.
8. Health Canada. Summary Safety Review - Bcr-Abl Tyrosine Kinase Inhibitors - Assessing the Potential Harm to the Fetus. 2 March 2016. Available at: <http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/>.
9. Donna Forrest MD. Personal communication. BC Cancer Agency Leukemia/Bone Marrow Transplant Tumour Group; 18 August 2009.
10. Judith Nyrose RPh. Personal communication. BC Cancer Agency Leukemia/Bone Marrow Transplant Tumour Group; 26 August 2009.
11. Novartis Pharmaceuticals Canada Inc. TASIGNA® product monograph. Dorval, Quebec; 21 December 2012.
12. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
13. Yin OQ, Bedoucha V, McCulloch T, et al. Effects of famotidine or an antacid preparation on the pharmacokinetics of nilotinib in healthy volunteers. *Cancer Chemother Pharmacol* 2013;701(1):219-226.
14. Yin OQP, Gallagher N, Fischer D, et al. Effect of the proton pump inhibitor esomeprazole on the oral absorption and pharmacokinetics of nilotinib. *J Clin Pharmacol* 2010;50(28):960-967.
15. Yin OQP, Giles FJ, Baccarani M, et al. Concurrent use of proton pump inhibitors or H2 blockers did not adversely affect nilotinib efficacy in patients with chronic myeloid leukemia. *Cancer Chemother Pharmacol* 2012;70(2):345-350.
16. Drug Interaction Facts (database on the Internet). Nilotinib. Facts and Comparisons 4.0, 2008. Available at: <http://online.factsandcomparisons.com>. Accessed 11 June 2009.
17. Novartis Pharmaceuticals Canada Inc. TASIGNA® product monograph. Dorval, Quebec; 28 November 2011.