

**DRUG NAME: Nilotinib****SYNONYM(S):** nilotinib hydrochloride monohydrate<sup>1</sup>**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.<sup>1</sup> This leads to selective inhibition of proliferation and induction of apoptosis.<sup>1</sup> 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).<sup>1,2</sup> Other targets include c-Kit and platelet derived growth factor receptor (PDGFR).<sup>3</sup> Nilotinib is cell cycle phase-nonspecific.<sup>1</sup> Nilotinib is an immunosuppressive agent.<sup>1</sup>

**PHARMACOKINETICS:**

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

Adapted from standard reference<sup>1</sup> unless specified otherwise.**USES:****Primary uses:**

\*Leukemia, chronic myelogenous

\*Health Canada approved indication

**Other uses:**Leukemia, acute lymphoblastic<sup>3</sup>**SPECIAL PRECAUTIONS:****Contraindications:**

- long QT syndrome<sup>1-3</sup>
- hypokalemia or hypomagnesemia<sup>1-3</sup>

**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<sup>1,2</sup>
- 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 therapy<sup>1</sup>
- concurrent medications should be reviewed carefully for potential interactions, particularly in regard to CYP 3A4, 2B6, 2C8, 2C9, 2D6, UGT1A1, and P-glycoprotein; see table and paragraphs in **Interactions** section.
- caution in patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia<sup>1</sup>
- hypokalemia, hypomagnesemia, and other electrolyte abnormalities must be corrected prior to beginning treatment and levels should be monitored periodically<sup>1,2</sup>
- 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<sup>1,2,4</sup>
- liver function and serum lipase should be monitored periodically during treatment, especially in those with a history of pancreatitis<sup>1,2</sup>

**Carcinogenicity:** no information found

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

**Fertility:** No effects noted in rat studies.<sup>1</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>3</sup> 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).

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>1-3</sup>

**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.<sup>5,6</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
blood/bone marrow/ febrile neutropenia	<b><i>anemia</i></b> (13%, severe 8-23%) <sup>1-3</sup> ; generally reversible
	febrile neutropenia (1-5%)
	<b><i>neutropenia</i></b> (15%, severe 28-37%) <sup>1-3</sup> ; generally reversible; median duration 15 days <sup>3</sup> ; see paragraph following <b>Side Effects</b> table
	<b><i>thrombocytopenia</i></b> (27%, severe 7-30%) <sup>1-3</sup> ; generally reversible; median duration 22 days <sup>3</sup> ; see paragraph following <b>Side Effects</b> table
	pancytopenia (1-5%)
cardiovascular (arrhythmia)	cardiac flutter
	extrasystoles
	palpitations (1-5%)
	<b><i>QT interval prolongation</i></b> (1-5%); see paragraph following <b>Side Effects</b> table

ORGAN SITE	SIDE EFFECT	
Clinically important side effects are in <b>bold, italics</b>		
cardiovascular (general)	congestive heart failure (1%)	
	hypertension (1-5%)	
	myocardial infarction	
	pericardial effusion (1%)	
	pericarditis	
ventricular dysfunction	ventricular dysfunction	
	constitutional symptoms	asthenia (6-14%) <sup>1,3</sup>
		<b>fatigue</b> (16-28%) <sup>1,3</sup>
		pyrexia (1-24%) <sup>1,3</sup>
		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%)	
	<b>pruritis</b> (20-29%) <sup>1,3</sup>	
	<b>rash</b> (26-33%) <sup>1,3</sup>	
	urticaria (1-5%)	
endocrine	<b>hyperglycemia</b> (severe 4-11%) <sup>1,3</sup>	
gastrointestinal	<i>emetogenic potential: low</i> <sup>7</sup>	
	abdominal discomfort (1-5%)	
	anorexia (5%)	
	<b>constipation</b> (11-21%) <sup>1,3</sup>	
	<b>diarrhea</b> (10-22%) <sup>1,3</sup>	
	dyspepsia (1-5%)	
	flatulence (1-5%)	
	<b>nausea</b> (18-31%) <sup>1,3</sup>	
vomiting (9-21%) <sup>1,3</sup>		
hemorrhage	CNS hemorrhage (1%)	
	gastrointestinal hemorrhage (3%)	
hepatobiliary/pancreas	<b>hepatotoxicity</b> , as evidenced by elevated alkaline phosphatase, ALT, AST, and bilirubin	
	<b>pancreatitis</b> (1%)	

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
lymphatics	peripheral edema (5-11%) <sup>1,3</sup>
metabolic/laboratory	albumin decreased (severe 1%)
	alkaline phosphatase increased (1-5%, severe 1-3%) <sup>1,3</sup>
	ALT increased (1-5%; severe 2-4%) <sup>1,3</sup>
	<b>amylase increased</b> (1-5%); see paragraph following <b>Side Effects</b> table
	AST increased (1-5%, severe 1%) <sup>1,3</sup>
	<b>bilirubin increased</b> (severe 9-10%) <sup>1,3</sup> ; the largest increases were observed in patients with UGT1A1*28 polymorphism <sup>2</sup>
	<b>blood glucose increased</b> (1-5%)
	creatinine phosphokinase increased (1-5%)
	gamma-glutamyltransferase increased (1-5%)
	hyperkalemia (severe 3-4%) <sup>1,3</sup>
	hypocalcemia (severe 1-4%) <sup>1,3</sup>
	hypokalemia (severe 1-5%) <sup>1,3</sup>
	hypomagnesemia (1-5%)
	hyponatremia (severe 3%)
	hypophosphatemia (severe 10%)
	<b>lipase increased</b> (>10%, severe 15-17%) <sup>1-3</sup> ; see paragraph following <b>Side Effects</b> table
musculoskeletal	<b>arthralgia</b> (6-18%) <sup>1,3</sup>
	muscle spasm (6-14%) <sup>1,3</sup>
	<b>myalgia</b> (8-14%) <sup>1,3</sup>
neurology	dizziness (1-5%)
	insomnia (1-5%)
	paresthesia (1-5%)
	vertigo (1-5%)
pain	abdominal (5-13%) <sup>1,3</sup>
	back (10-12%) <sup>3</sup>
	bone (6-13%) <sup>1,3</sup>
	<b>headache</b> (15-31%) <sup>1,3</sup>
	limb (13-16%) <sup>3</sup>
	musculoskeletal (1-5%)
	musculoskeletal, chest (1-5%)
pulmonary	cough (1-17%) <sup>1,3</sup>
	dyspnea (1-11%) <sup>1,3</sup>
	dyspnea on exertion (1-5%)
	dysphonia (1-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
	nasopharyngitis (11-16%) <sup>3</sup>
	pleural effusion (1%)

Adapted from standard reference<sup>1</sup> unless specified otherwise.

**QT interval prolongation** may occur, which may in turn result in torsades de pointes, leading to syncope, seizure, and/or death.<sup>1-3</sup> **Sudden deaths** have been reported (0.1-1%); ventricular repolarization abnormalities may have contributed.<sup>1,2</sup> Prolongation is concentration-dependent.<sup>2</sup> 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.<sup>1</sup> The presence of hypokalemia and hypomagnesemia may further enhance this effect.<sup>1</sup> If the QT interval corrected for rate (QT<sub>c</sub>) exceeds 480 msec, nilotinib should be withheld.<sup>2,3</sup>

- If, within two weeks, the QT<sub>c</sub> returns to less than 450 msec and to within 20 msec of baseline, nilotinib may be resumed at the prior dosage.<sup>2,3</sup>
- If, after two weeks, the QT<sub>c</sub> is between 450 and 480 msec, nilotinib may be resumed at a reduced dose of 400 mg once daily.<sup>2,3</sup>
- If QT<sub>c</sub> exceeds 480 msec after this dose reduction, nilotinib should be discontinued.<sup>2,3</sup>

**Neutropenia and/or thrombocytopenia** that is not related to the underlying CML may necessitate treatment interruption or dosage reduction.<sup>2</sup> Complete blood counts should be monitored every one to two weeks during the first two months of therapy and at least monthly thereafter.<sup>1,2,4</sup> Hold nilotinib if ANC less than 1 x 10<sup>9</sup> and/or platelets less than 50 x 10<sup>9</sup>.<sup>2</sup> 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.<sup>2</sup>

**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.<sup>3</sup> 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.<sup>3</sup>

**INTERACTIONS:**

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice <sup>1,2,8</sup>	may increase nilotinib plasma level	may inhibit CYP 3A4 metabolism of nilotinib in the intestinal wall	avoid grapefruit and grapefruit juice
ketoconazole <sup>1,2</sup>	three-fold increase in nilotinib AUC	CYP 3A4 inhibition	avoid ketoconazole or consider reducing nilotinib dose
midazolam <sup>1,2</sup>	midazolam exposure increased by 30% (single dose)	CYP 3A4 inhibition by nilotinib	anticipate increased effect; consider dose adjustment
rifampin <sup>2</sup>	80% decrease in nilotinib AUC	CYP 3A4 induction	avoid rifampin or consider increasing nilotinib dose, with close monitoring of QT interval
warfarin <sup>2</sup>	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.<sup>1-3</sup>

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.<sup>1-3</sup>

CYP 3A4 inducers may reduce exposure to nilotinib; increase of nilotinib dose should be considered.<sup>1,2</sup>

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

Nilotinib inhibits CYP 3A4, 2C8, 2C9, 2D6, UGT1A1, and P-glycoprotein.<sup>2,3</sup>

Nilotinib induces CYP 2B6, 2C8, 2C9.<sup>2,3</sup>

**SUPPLY AND STORAGE:**

**Oral:** Novartis supplies nilotinib as 150 mg and 200 mg capsules, containing lactose. Store at room temperature, in original packaging.<sup>9</sup>

**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*<sup>1,2,4</sup>:

***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.<sup>1-3</sup>

Swallow whole with water.<sup>1-3</sup> Take doses approximately 12 hours apart.<sup>2,3</sup>

*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 recommended<sup>3</sup>:

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

*Dosage in renal failure:*

Dose adjustment likely not required.<sup>1,2</sup>

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

*Dosage in hepatic failure:* Metabolism is mainly hepatic; increased exposure can be expected in patients with hepatic impairment.<sup>1,2</sup> 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).<sup>2,3</sup>

*Dosage in dialysis:* no information found

**Children:**

*Oral:* No clinical studies conducted in children and adolescents.<sup>1</sup> Safety and efficacy not established.<sup>3</sup>

**REFERENCES:**

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