Drug Monograph

A - Drug Name

niLOtinib

COMMON TRADE NAME(S): Tasigna®

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B - Mechanism of Action and Pharmacokinetics

The Philadelphia chromosome is created by a reciprocal translocation between chromosomes 9 and 22, and results in production of a constitutively activated kinase (Bcr-Abl tyrosine kinase). Nilotinib is an inhibitor of Bcr-Abl in Philadelphia-chromosome positive (Ph+) leukemia cells. It is an aminopyrimidine derivative of imatinib, and is approximately 30 times more potent than imatinib. Nilotinib also inhibits the tyrosine kinase of platelet-derived growth factor (PDGF) receptor, c-KIT and DDR. It maintains activity against 32 of 33 imatinib-resistant mutant forms of Bcr-Abl, except for T315I.

Absorption	Peak concentrations are reached at 3 hours with steady state achieved by day 8. Higher exposure in females has been observed (20% higher than males.)	
	Bioavailability	The bioavailability is approximately 30%, reduced by 48% in patients with total gastrectomy. When administered 30 min after food, the bioavailability increased by 29%.
Distribution	Mainly distributed to liver, adrenal cortex, small intestine, uveal tract	
	Cross blood brain barrier?	Minimal
	PPB	98 %

Metabolism	Extensive metabolism by CYP3A4, also a substrate for P-glycoprotein (Pgp).	
	Active metabolites	None
	Inactive metabolites	Carboxylic acid derivative and other metabolites
Elimination	Urine	Parent drug and metabolites: minimal
	Feces	>90% of the dose within 7 days
	Half-life	17 hours

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C - Indications and Status

Health Canada Approvals:

- Treatment of adult patients with newly diagnosed Ph+ CML in chronic phase
- The treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib

Note:

Approval for use in newly diagnosed patients was based on the observation of major molecular and cytogenetic responses; overall survival benefit has not been demonstrated.

Approval for imatinib resistant or intolerant patients was based on hematological and unconfirmed major cytogenetic response rates.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported mainly in patients with newly diagnosed CML, receiving nilotinib 300 mg BID.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<5%)	E
	Arterial thromboembolism (3%)	E
	Cardiotoxicity (<5%)	E D
	Hypertension (<5%)	E
	Pulmonary hypertension (rare)	E
	QT interval prolonged (14%) (QT>450msec)	E
	Sudden death (rare)	E
	Venous thromboembolism (<1%)	E
Dermatological	Alopecia (10%)	E
	Photosensitivity (rare)	E
	Rash (33%) (may be severe)	E
Gastrointestinal	Abdominal pain (10%)	E
	Anorexia (4%)	E
	Constipation (10%)	E
	Diarrhea (9%)	E
	Dyspepsia (5%)	E
	GI perforation (rare)	E D
	Mucositis (<1%)	E
	Nausea, vomiting (14%)	E
General	Fatigue (13%)	E
	Fever (<5%)	E
	Fluid retention (5%) (may be severe, including effusions 1%)	E
Hematological	Myelosuppression ± infection, bleeding (grade 3-4; 12%) (including GI/CNS bleeding)	E
Hepatobiliary	↑ Amylase / lipase (grade 3-4: 8%)	E

	↑ LFTs (4%) (grade 3-4, may be severe)	E
	Pancreatitis (2%)	E
Hypersensitivity	Hypersensitivity (rare)	E
Immune	Other Atypical infections including HBV reactivation	D
Metabolic / Endocrine	Abnormal electrolyte(s) (5%) (grade 3-4, for ↑ / ↓ K, Na, Ca, Mg, Phosphate)	E
	↑ Cholesterol (3%)	E
	Hyperglycemia (6%) (grade 3/4)	E
	Hyperlipidemia (<5%) (<1% severe with 400mg daily)	E
	Hyperthyroidism (<1%)	E D
	Hypothyroidism (<1%)	E D
	Tumour lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (10%)	E
	↑CPK (<5%)	E
	Rhabdomyolysis (rare)	E
Neoplastic	Secondary malignancy (rare; GI, ovarian, pNET, skin)	
Nervous System	Dizziness (<5%)	E
	Dysgeusia (<5%)	E
	Headache (16%)	E
	Insomnia (<5%)	E
	Mood changes (<5%)	E
	Neuropathy (<5%)	E
	Optic neuritis (rare)	E
	Vertigo (<5%)	E
Ophthalmic	Conjunctivitis (<5%)	E
Renal	Creatinine increased (rare, may be severe)	E
Respiratory	Cough, dyspnea (<5%)	E
	Interstitial lung disease (rare)	E
	Pneumonitis (<1%)	E
Urinary	Urinary symptoms (<5%)	E
Vascular	Vasculitis (rare)	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 frequently reported drug-related adverse events are **myelosuppression, headache, fatigue, myalgia, rash, pruritus, GI side effects.** Myelosuppression is more frequent in patients with advanced or refractory disease.

Increases in serum **lipase/amylase** have been observed, in which a few were associated with abdominal pain or pancreatitis. Increases in LFTs have been reported, and rarely, fatal hepatic failure. Patients with Gilberts may have increases in their unconjugated bilirubin.

Nilotinib may **prolong the QT interval**, and should be used with caution in patients at risk, such as those with hypokalemia, hypomagnesemia, those on antiarrhythmic therapy or other medications that may prolong the QT interval, or patients who have received cumulative high-dose anthracyclines. Administering with meals or strong CYP3A4 inhibitors significantly increases the risk. Hypokalemia or hypomagnesemia must be corrected prior to nilotinib therapy. Patients with uncontrolled or significant cardiac disease were excluded from clinical trials; there was no clinically significant change in LVEF from baseline in previously untreated patients. (See Special Precautions and Interactions sections.)

Peripheral arterial occlusive disease, **ischemic heart disease and ischemic cerebrovascular events** have been reported, may be fatal, and are more common in patients with risk factors. Patients should be monitored for signs and symptoms of atherosclerosis, including monitoring lipid and glucose profiles (see Monitoring). Peripheral arterial occlusive disease can be severe, rapidly progressing, affect more than one site and require repeated revascularization procedures.

Severe **fluid retention**, including pleural and pericardial effusion/tamponade and pulmonary edema has been reported. Unexpected, rapid weight gain should be investigated and treated appropriately.

Reactivation of hepatitis B virus (HBV) has been reported in patients who received BCR-ABL TKI's and are chronic carriers of HBV. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Patients should be tested for HBV infection prior to initiating treatment. Consult hepatology/infectious disease if seropositive. Carriers of HBV must be monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

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E - Dosing

Refer to protocol by which 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.

Hypokalemia and hypomagnesemia must be corrected prior to starting treatment with nilotinib. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Avoid concomitant use of antiemetics. BID doses should be taken at approximately 12 hour intervals, 1 hour before or 2 hours after food.

Adults:

Newly diagnosed Ph+ CML-CP:

Oral: 300 mg BID

Resistant or Intolerant Ph+ CML-CP or CML-AP:

Oral: 400 mg BID

Dosage with Toxicity:

Dosage with hematologic toxicities: Exclude underlying disease causality.

Counts (X 10^9/L)	**Action**		**Time required for recovery (Platelets > 50 X 10^9/L and/or ANC > 1 X 10^9/L)**	**Subsequent Dose**
ANC < 1 and/or Platelet counts <50	Hold and monitor counts	AND	≤ 2 weeks	Resume at prior dose
			> 2 weeks	Restart at 400mg once daily

Dosage with QT prolongation:

QTc	Action		QTc monitoring	Subsequent Dose
QTc > 480 msec	Hold; correct hypokalemia and hypomagnesemia. Review concomitant medications.	AND	QTcF < 450 msec or within 20 msec of baseline within 2 weeks	Resume at prior dose
			QTcF = 450 – 480 msec after 2 weeks	Restart at 400mg once daily*
			No recovery	Discontinue
QTc > 480 msec at 400mg daily	Discontinue	-	-	-

*repeat ECG 7 days after any dosage adjustment

Dosage with non-hematologic toxicities:

Toxicity	Action
≥ Grade 3 LFTs or ↑ lipase / amylase	Hold; resume at 400mg once daily when ≤ Grade 1
Symptomatic lipase or amylase ↑	Hold, investigate. May resume at 400mg once daily if ≤ grade 1
Other clinically significant moderate, or severe (≥ Grade 3, including fluid retention)	Hold; resume at 400mg once daily when resolved. Consider re-escalation to starting dose if clinically appropriate.

Dosage with Hepatic Impairment:

Increased nilotinib exposure was observed in patients with hepatic impairment. Clinical studies excluded patients with ALT/AST > 2.5 x ULN and total bilirubin > 1.5 x ULN.
Dose adjustment is not required for mild to moderate hepatic impairment at baseline. Use with caution; monitor LFTs and QTc interval regularly. Consider dose reduction in patients with severe impairment and use with extreme caution. Use the table above for hepatic toxicity.

Dosage with Renal Impairment:

Nilotinib and its metabolites are minimally excreted by the kidney. Although dose adjustments are not anticipated, patients with creatinine > 1.5 x ULN were excluded from clinical trials. Patients with renal impairment may be at increased risk of TLS.

Dosage in the elderly:

No differences in safety and efficacy were observed in patients ≥ 65 years of age.

Children:

The safety and effectiveness of nilotinib in children and adolescents have not been studied.

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F - Administration Guidelines

- Nilotinib should be swallowed whole with a glass of water on an empty stomach, at least 1 hour before and 2 hours after food.
- If patient has trouble swallowing the capsules, may open the capsule and mix the content of each capsule in 1 teaspoon of applesauce and swallow immediately. Do not mix with other foods or liquids or use more applesauce than described above.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- If a dose is missed, take the next dose as scheduled. Do not replace missed doses.
- Store at room temperature (15-30°C) in the original package

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to nilotinib or to any of its excipients
- Long QT syndrome, persistent QT_C > 480 msec
- Uncorrectable hypokalemia or hypomagnesemia

Other Warnings/Precautions:

- The risk of QT prolongation is increased when nilotinib is taken with food, in patients who have had high-dose anthracyclines, patients with uncontrolled or significant cardiac disease (i.e. MI, CHF, unstable angina, etc) or with hypokalemia or hypomagnesemia.
- Avoid drugs that can prolong QT including antiemetics, antiarrhythmics and strong CYP3A4 inhibitors (Refer to Interactions section).
- Exercise caution in patients with risk factors for atherosclerosis.
- Use with caution in patients with risk of tumour lysis (high tumour burden or decreased renal function).
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients with Gilbert's Syndrome may experience an ↑ in indirect bilirubin levels.
- Caution is recommended in patients with hepatic impairment or a previous history of pancreatitis.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Crosses placental barrier: Documented in animals
- Pregnancy:
  Nilotinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **4 weeks** after the last dose.
- Excretion into breast milk: Documented in animals
  Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Probable
  Documented in animal studies

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H - Interactions

Nilotinib is an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, UGT1A1 and inducer of CYP2B6, CYP2C8, and CYP2C9. This may result in interactions with substrates of these enzymes (i.e. increased exposure to HMG CoA reductase inhibitors, or statins).

Nilotinib absorption is increased when taken with food, which can result in higher serum concentrations and toxicity (e.g. prolonged QT interval; see Administration section)

Yogurt has been shown to result in significant increases in nilotinib bioavailability. Do not use yogurt to disperse the capsule contents (see Administration Guidelines section).

Avoid concomitant use of **antiemetics**, including metoclopramide, prochlorperazine, ondansetron, dolasetron and others that may prolong the QT interval.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ nilotinib concentration, increase risk of QT prolongation (up to 3-fold)	↓ metabolism	Avoid concomitant use – interrupt nilotinib; if not feasible, monitor QTc closely
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ nilotinib concentration (up to 80%)	↑ metabolism	Avoid concomitant use
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ plasma concentration of CYP3A4 substrates (up to 3-fold)	Nilotinib is moderate CYP3A4 inhibitor	Monitor; consider dose adjustment for CYP3A4 substrates with narrow therapeutic index
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ concentration of Pgp substrates	Pgp inhibition by nilotinib	Caution; consider use of alternative medications

P-glycoprotein inhibitors (i.e. quinidine, cyclosporine)	↑ nilotinib concentration and/or toxicity	nilotinib is a Pgp substrate	Caution
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Avoid; monitor closely if must use
Proton Pump Inhibitors, prior gastrectomy	↓ nilotinib concentration	Suppression of gastric acid decreases bioavailability of nilotinib	Use proton inhibitors as needed with caution
Non absorbable Antacids (aluminum hydroxide/magnesium hydroxide/simethicone)	↓ nilotinib concentration	Suppression of gastric acid decreases bioavailability of nilotinib	Administer ≥ 2 hours before or after nilotinib
H2 blockers	↓ nilotinib concentration	Suppression of gastric acid decreases bioavailability of nilotinib	Give H2 blockers 10 hours before or 2 hours after nilotinib
Alcohol	One report of reduced efficacy with concomitant use	Unknown	Avoid
CYP2D6 substrates (e.g. beta-blockers, tramadol, nortriptyline, mirtazapine, serotonin-H3 antagonists)	↑ plasma concentration of CYP2D6 substrates	nilotinib appears to inhibit CYP2D6 enzymes	Caution
CYP 2B6 substrates (i.e. bupropion, cyclophosphamide, selegiline)	↓ plasma concentration of CYP2B6 substrates	Nilotinib appears to induce CYP2B6 enzymes	Caution

UGT1A1 substrates (i.e. estradiol, irinotecan)	↑ concentration of UGT1A1 substrates	Nilotinib appears to inhibit UGT1A1	Caution
CYP 2C9 substrates (e.g. warfarin, glyburide, losartan, diclofenac)	↑ plasma concentration of CYP2C9 substrates (e.g. enhanced warfarin effect) or ↓ plasma concentration of CYP2C9 substrates	Nilotinib appears to inhibit CYP2C9 and/or induce CYP2C9	Caution; monitor carefully and adjust warfarin dose accordingly closely
CYP 2C8 substrates (i.e. paclitaxel, sorafenib, amiodarone)	↓ (or ↑) plasma concentration of CYP2C8 substrates	Nilotinib appears to induce (and/or inhibit) CYP2C8	Caution
Drugs that may alter electrolyte levels (e.g. diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of QT prolongation	altered electrolyte levels	Caution; monitor closely

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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
Fasting blood glucose, lipid profile and creatine kinase (CK)	baseline, regular, and as clinically indicated
Renal function tests	baseline and regular
Electrolytes, including phosphorus, potassium, calcium and magnesium	baseline and regular
Liver function tests	baseline and regular, also monitor following dose adjustments or as clinically indicated
Lipase, amylase; baseline and regular	also monitor following dose adjustments or as clinically indicated

ECG	baseline, seven days after initiation and following dose adjustments, then periodically thereafter
CBC	Baseline and regular; every 2 weeks for the first 2 months and then monthly, or as clinically indicated
Monitoring for tumor lysis syndrome (including phosphate, uric acid, LDH)	baseline and initial treatment period until tumour burden significantly reduced
Weight and other signs and symptoms of fluid retention	Baseline and regular
Clinical assessment of toxicity (e.g. GI effects, fluid retention, rash, hemorrhage, cardiovascular, infection, hyperglycemia, pneumonitis, etc.)	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Close INR monitoring for patients on warfarin	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- niLOtinib - Accelerated phase Ph+ CML with documented resistance or intolerance to imatinib therapy, with specific criteria
- niLOtinib - Chronic phase Ph+ CML, with specific criteria

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K - References

BCR-ABL Tyrosine Kinase Inhibitors [GLEEVEC (imatinib mesylate), TASIGNA (nilotinib), BOSULIF (bosutinib), SPRYCEL (dasatinib), ICLUSIG (ponatinib hydrochloride)] - Risk of Hepatitis B Reactivation. Health Canada, May 4, 2016. [Accessed May 13, 2016]. Available from: http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/58222a-eng.php

Jarkowski A, Sweeney RP. Nilotinib: A New Tyrosine Kinase Inhibitor for the Treatment of Chronic Myelogenous Leukemia. Pharmacotherapy 2008;28(11):1374-82.

Plosker GL, Robinson DM. Nilotinib. Drugs 2008;68 (4):449-59.

Product Monograph: Tasigna® (nilotinib). Novartis Pharmaceuticals Canada, August 25, 2016.

Product Monograph: Tasigna® (nilotinib). Novartis Pharmaceuticals Canada, July 17, 2024.

July 2025 Updated Pregnancy/Lactation 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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