Drug Monograph

A - Drug Name

SORAfenib

COMMON TRADE NAME(S): Nexavar®

back to top

B - Mechanism of Action and Pharmacokinetics

Sorafenib is a multikinase enzyme inhibitor that decreases cell proliferation in vitro. Sorafenib blocks Raf kinase and inhibits tumour angiogenesis by blocking activation of involved receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR 1, 2 and 3), platelet-derived growth factor receptor-beta (PDGFRβ), FLT3, c-KIT and RET.

Absorption	Oral absorption: Yes Peak plasma levels are reached approximately 3 hours after an oral dose. Pharmacokinetics are less than dose proportional at doses > 400 mg BID. Daily dosing results in a 2.5-to 7-fold accumulation at steady state, which is reached within 7 days. Age, gender, or body weight does not appear to affect sorafenib pharmacokinetics.	
	Bioavailability	38-49%; ↓ by 29% with high fat meal. Exposure is 70% higher in DTC compared to RCC or HCC patients (clinical relevance not clear).
Distribution	Sorafenib is extensively plasma protein bound.	
	Cross blood brain barrier?	No information found (unlikely)
	PPB	99.5%

Metabolism	Sorafenib is metabolized primarily in the liver by CYP3A4 and is glucuronidated by UGT1A9.	
	Active metabolites	Pyridine N-oxide
	Inactive metabolites	yes
Elimination	Sorafenib is eliminated predominantly by fecal excretion (77% of dose within 14 days, 51% unchanged).	
	Urine	19% of dose within 14 days, as metabolites
	Half-life	25 - 48 hours

back to top

C - Indications and Status

Health Canada Approvals:

• Treatment of locally advanced/metastatic clear cell renal cell carcinoma (RCC) in patients who have failed or are intolerant of prior systemic therapy
• Treatment of patients with unresectable hepatocellular carcinoma (HCC)
• Treatment of patients with locally advanced or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine

Notes:

Health Canada approval for low or intermediate risk (MSKCC) clear cell renal cell cancer was based on an increase in progression-free survival, while approval for hepatocellular carcinoma (HCC) was based on overall survival. For hepatocellular carcinoma, the pivotal trial included mainly patients with Child-Pugh A; data from other studies suggest that Child-Pugh B patients have significantly poorer outcomes and the benefit of sorafenib in these patients is as yet to be defined. Approval for differentiated thyroid carcinoma (DTC) was based on improvements in progression-free survival; an overall survival benefit was not established.

Other Uses:

- Acute myeloid leukemia (for FLT3-ITD positive patients only)

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table contains adverse effects reported mainly in monotherapy in patients with RCC, where the incidence was greater in the treatment arm than in the placebo arm.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (3%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Cardiotoxicity (2%)	E D
	Hypertension (17%) (may be severe)	E
	QT interval prolonged (rare)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (27%)	E
	Hand-foot syndrome (30%)	E
	Radiation recall reaction (rare)	E
	Rash (40%) (may be severe)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia, weight loss (16%)	E
	Constipation (15%)	E
	Diarrhea (43%)	E
	Dyspepsia (<10%)	E
	Dysphagia (<10%)	E
	GI perforation (rare)	E
	Mucositis (11%)	E
	Nausea, vomiting (24%)	E
General	Fatigue (37%)	E
Hematological	Hemorrhage (15%) (including GI, respiratory, CNS)	E

	INR / prothrombin time increased (5%) (grade 3)	E
	Myelosuppression ± infection, bleeding (44%) (2% severe)	E
Hepatobiliary	↓ albumin (27%)	E
	↑ Amylase / lipase (41%) (grade 3/4: 12%)	E
	Cholecystitis (<10%)	E
	Hepatitis (drug induced; rare)	E
	↑ LFTs (30%) (may be severe)	E
	Pancreatitis (<1%)	E
Hypersensitivity	Hypersensitivity (<1%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (45%) ↓ PO4 , ↓ Na, ↓ Ca, ↑/↓K (severe up to 13%)	E
	Hyperthyroidism (rare)	E
	Hypothyroidism (<10%)	E
Musculoskeletal	Musculoskeletal pain (10%)	E
	Osteonecrosis of jaw (rare)	E
	Rhabdomyolysis (rare)	E
Neoplastic	Secondary malignancy (5%) (keratoacanthoma/squamous cell carcinoma of the skin in DTC patients)	D
Nervous System	Depression (<10%)	E
	Headache (10%)	E
	Posterior reversible encephalopathy syndrome (PRES) (reversible posterior encephalopathy; rare)	E
	Sensory neuropathy (13%)	E
Renal	Proteinuria (<10%)	E
	Renal failure (rare)	E
Respiratory	Cough, dyspnea (14%)	E
	Dysphonia (9%)	E
	Pleural effusion (4%)	E
	Pneumonitis (rare)	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 in clinical trials were: **rash/desquamation, diarrhea, hand-foot skin reaction, fatigue, hypertension, alopecia, weight loss, nausea, abdominal pain, anorexia, infection and hemorrhage.**

Most adverse reactions were reported more frequently in the DTC population and more likely to be dose-limiting.

Hypertension was usually mild-moderate, generally occurred early in the course of treatment and amenable to standard antihypertensive therapy. (For suggested treatment algorithm, see Appendix 8: Management of Angiogenesis Inhibitor (AI) Induced Hypertension).

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

Management of **hand-foot syndrome** and rash/desquamation (typically occurring within the first 12 weeks of therapy) may include topical treatment for symptomatic relief and temporary interruption and/or sorafenib dose modification. In severe or persistent cases, permanent discontinuation of sorafenib may be necessary. Severe rashes including SJS, TEN and leucocytoclastic vasculitis have been described.

Elevated lipase and amylase levels, typically transient, were commonly reported. Clinical pancreatitis has been reported.

Drug-induced hepatitis has been reported rarely. Typical onset is 10-90 days following treatment initiation and is generally reversible, but may result in fatal liver failure.

Hemorrhage, including all sites, occurred in 15% of patients compared to 8% in placebo patients. Permanent discontinuation of sorafenib should be considered if any bleeding event necessitates medical intervention.

Sensory neuropathy events were usually mild to moderate and tended to occur in the first few cycles of treatment.

Gastrointestinal perforation is uncommon, but may occur in the absence of an intra-abdominal tumour.

Cardiac ischemia and infarction (ATE) occurred at a higher frequency than in the placebo arms; patients with unstable angina or recent infarction (within 6 months) were excluded from the clinical trials.

Osteonecrosis of the jaw has been reported rarely. Avoid invasive dentistry during treatment, especially in patients with prior bisphosphonate exposure.

Changes in thyroid function have been observed, with **hypothyroidism** observed more commonly.

back to top

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, hypomagnesemia and hypocalcemia should be corrected before sorafenib treatment.

Patients with DTC should have esophageal and upper airway infiltration controlled with local measures prior to starting treatment to reduce the risk of bleeding.

Adults:

Oral: 400 mg twice daily on an empty stomach or with a low-fat or moderate-fat meal

Dosage with Toxicity:

Dose levels:

Dose level	Sorafenib dose
0	800mg daily dose (400mg bid)
-1	600mg daily dose (400mg and 200mg, 12 hours apart)
-2	400mg daily dose (200mg bid)
-3	200mg daily dose (200mg od)

Dosage with toxicity for HCC and RCC populations:

Toxicity grade	Occurrence	Dose modification
Grade 1 skin	Any	Continue treatment with sorafenib and consider topical/supportive therapy for symptomatic relief.
Grade 2 skin	1st	Continue treatment, supportive care. Consider ↓ 2 dose levels for 28 days; if does not improve hold for at least 7 days until ≤ grade 1 and restart at 400mg daily. If ≤ grade 1 x 28 days, consider re-escalating to full dose.

	2nd or 3rd	As for 1st occurrence, but do no re-escalate if hold required.
	4th	Consider discontinuing sorafenib.
Grade 3 skin	1st	Supportive care and hold at least 7 days until ≤ grade 1, restart by ↓ 2 dose levels; if ≤ grade 1 x 28 days, consider re-escalating to full dose.
	2nd	As for 1st occurrence, but do not re-escalate.
	3rd	Consider discontinuing sorafenib.
Grade 3 non-hematological/related organ	1st	Hold until recovery to ≤ grade 2; ↓ 2 dose levels
	2nd	Discontinue
Cardiac ischemia and/or infarction	Any	Hold; consider discontinuing
↑LFTs	Any	Hold if severe and rule out other causes. Discontinue if drug-induced hepatitis.
GI perforation, severe hypertension despite treatment, cardiac failure, ≥ grade 3 bleeding, pneumonitis, SJS or TEN, Grade 4 non-hematological/related organ	Any	Discontinue

Dosage with toxicity for DTC population:

Toxicity Grade	Occurrence	Dose Modification*
Grade 1 Skin	Any	Continue treatment with sorafenib and consider topical / supportive therapy for symptomatic relief.
Grade 2 Skin	1st	Continue treatment, supportive care. Consider ↓1 dose level. If no improvement within 7 days, hold until ≤ grade 1, then ↓ 1 dose level.

	2nd	hold until resolved to ≤ grade 1. Resume by ↓ 1 dose level.
	3rd	Hold until resolved to ≤ grade 1. Resume by↓ 2 dose levels.
	4th	Discontinue
Grade 3 skin	1st	Hold until resolved to ≤ grade 1. Resume by ↓ 1 dose level
	2nd	Hold until resolved to ≤ grade 1. Resume by ↓ 2 dose levels.
	3rd	Discontinue
Grade 3 non hematological/organ	1st	Hold until recovery to ≤ grade 2, Resume by ↓ 2 dose levels.
	2nd	Discontinue
Cardiac ischemia and/or infarction;	Any	Hold. Consider discontinuing.
↑ LFTs	Any	Hold if severe and rule out other causes. Discontinue if drug-induced hepatitis.
GI perforation; Severe hypertension despite treatment; Cardiac failure; ≥grade 3 bleeding; Pneumonitis; SJS or TEN; Grade 4 non-hematological/organ	Any	Discontinue
*For patients who require a dose reduction for Grade 2 or 3 skin toxicity, dose may be increased if improved to ≤ grade 1 after 28 days of treatment at reduced dose.		

Dosage with Hepatic Impairment:

Patients with hepatocellular carcinoma (HCC) and Child-Pugh B hepatic impairment have greater systemic exposure than Child-Pugh A patients, although this difference is not seen in non-HCC patients. Exercise caution and monitor closely when treating Child-Pugh B patients with sorafenib, due to the heterogenous nature of this population. Sorafenib has not been studied in patients with Child Pugh C hepatic impairment.

(Continued on next page)

Miller 2009 suggested the following dose modifications in patients with HCC:

Child-Pugh		Bilirubin	Albumin	Dose
A	AND	≤ 1.5 x ULN		400mg bid
B	AND/OR	> 1.5 - 3 x ULN		200mg bid
C	AND/OR	> 3 x ULN		Do not treat – severe toxicity likely
			≤ 25	200mg daily

Dosage with Renal Impairment:

Although the product monograph suggests that no dose adjustments are required in patients with mild, moderate, or severe renal impairment not requiring dialysis, a pharmacokinetic study (Miller 2009) suggested the following:

Creatinine clearance	Dose
> 40 mL/min	400mg BID
20-40 mL/min	200mg BID
< 20mL/min	No information; avoid or use with extreme caution

Dosage in the elderly:

Dosage adjustment is not necessary in elderly patients.

Children:

Safety and effectiveness in children have not been established.

back to top

F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Prescribed dose should be administered orally on an empty stomach, or with a low-fat or moderate-fat meal with a large glass of water
- Store at room temperature (15-30°C)

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Concomitant warfarin or antiplatelet agents should be used cautiously
- Temporary hold is recommended for patients undergoing major surgery
- Hypokalemia, hypomagnesemia and hypocalcemia should be corrected before treatment
- Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with localized therapy before starting sorafenib in DTC patients.
- Sorafenib may impair exogenous thyroid suppression in DTC patients.
- Sorafenib should be administered with caution in patients who have bradycardia or with increased risk of developing prolongation of the QT interval/torsades de pointes (i.e. hypokalemia or hypomagnesemia, congenital long QT syndrome, history of cardiac disease or arrhythmias, concomitant anti-arrhythmic or other medications that may prolong QT interval). Patients with unstable coronary artery disease or recent MI (within 6 months) were excluded from clinical trials.

Pregnancy and Lactation:

- Teratogenicity: Yes
  Sorafenib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 2 weeks after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Yes
  Sorafenib impairs male and female fertility.

back to top

H - Interactions

Sorafenib does not inhibit or induce CYP 3A4, 2D6 or 2C19, but does inhibit CYP2B6 and 2C8 and is a substrate for CYP3A4.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP2B6 substrates (cyclophosphamide, ifosfamide, methadone, bupropion etc.) and CYP2C8 substrates (paclitaxel etc.)	May ↑ concentration of substrates	Sorafenib inhibits CYP2B6 and CYP2C8	Caution
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	May ↓ Sorafenib concentrations	↑ metabolism	Caution; Avoid concurrent use of a strong CYP3A4 inducer
Doxorubicin	↑ doxorubicin AUC (21%)	Unknown	Caution. Monitor for symptoms of doxorubicin toxicity.
Drugs metabolised by UGT1A1 and UGT1A9 (irinotecan etc.)	↑ exposure of substrates (irinotecan and SN-38 AUC ↑ 120%)	Inhibition of UGT1A1 pathway-mediated irinotecan and SN-38 metabolism	Caution. Monitor for irinotecan toxicity.
docetaxel	↑ docetaxel AUC (80%)	Unknown	Use with Caution.
neomycin	↓ sorafenib (54%) bioavailability	Neomycin interferes with enterohepatic recycling of sorafenib	Avoid concomitant use
warfarin	↑ INR reported, Bleeding	Possible additive effect; low risk suggested for clinically relevant CYP2C9 inhibition by sorafenib	Regular monitoring of INR and bleeding
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine,	↑QT/QTc prolonging effect	Additive	Avoid concomitant use

amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)			
capecitabine	↑ capecitabine exposure (50%)	Unknown	Caution
Paclitaxel/Carboplatin combination	↑ sorafenib and paclitaxel exposure	Unknown	Avoid concomitant use
UGT1A9 inhibitors (eg. erlotinib, mefanamic acid, ketoconazole, atorvastatin)	↑ sorafenib concentrations (theoretical)	Inhibits UGT1A9 mediated sorafenib glucuronidation	Caution
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	May ↑ sorafenib concentrations (theoretical) (Exposure not altered with ketoconazole and single sorafenib 50mg dose)	↓ metabolism	Caution
Exogenous thyroid suppression (e.g. levothyroxine) in DTC patients	impaired thyroid suppression	sorafenib inhibition	Caution; monitor TSH

back to top

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
Blood pressure	Weekly for first 6 weeks of treatment, then periodically thereafter
INR, for patients on warfarin	regular, especially at initiation, or discontinuation or change of dose.
CBC	Baseline and at each visit
Liver function tests, amylase and lipase	Baseline and regular
ECG during therapy (to monitor QT)	Baseline and periodic
Electrolytes, including phosphate and calcium	Baseline and regular
In patients with DTC, close monitoring of blood calcium and TSH levels	Baseline, monthly and as clinically indicated
Thyroid function tests	Baseline and regular
Clinical toxicity ratings (bleeding, hypertension, skin changes, diarrhea, pancreatitis, congestive heart failure, hepatitis, secondary malignancies)	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
LVEF, especially in patients with cardiac risk factors	Baseline and periodic
Dental evaluation before starting treatment with preventative dentistry as needed	

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- SORAfenib - Metastatic renal cell carcinoma of clear cell histology as second-line treatment, with specific criteria
- SORAfenib - Advanced hepatocellular carcinoma, with specific criteria

back to top

K - References

Cheng AL, Kang YK, Chen ZD, et al. Efficacy and safety of sorafenib in patients in the Asia-pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncology 2009;10:25-34.

Escudier B, Eisen T, Stadler WM, et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. N Engl J Med 2007;356:125-34.

Hollebecque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34(10):1193-201.

Lencioni R, Kudo M, Ye SL, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib) non-interventional study. Int J Clin Pract 2012;66(7):675-83.

Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced heptatocellular carcinoma. NEJM 2008:359;378-90.

Miller AA, Murry DJ, Owzar K et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. J Clin Oncol 2009;27(11):1800-5.

Pinter M, Sieghart W, Graziadel I, et al. Sorafenib in Unresectable Hepatocellular Carcinoma from Mild to Advanced Stage Liver Cirrhosis. Oncologist 2009;14(1):70-6.

Prescribing Information: Nexavar® (sorafenib). Bayer Healthcare Pharmaceuticals Inc. (US), December 2012.

Pressiani T, Boni C, Rimassa L, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013;24(2):406-11.

Product Monograph: Nexavar® (Sorafenib). Bayer Inc., December 17, 2014.

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

Sorafenib and osteonecrosis of the jaw. Canadian Adverse Drug Reaction Newsletter, volume 24, no. 4, October 2014. [Accessed: October 30, 2014]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v24n4-eng.php#article3

Wörns MA, Weinmann A, Pfingst K, et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009;43(5):489-95.

Zhu AX, Clark JW. Commentary: Sorafenib Use in Patients with Advanced Hepatocellular Carcinoma and Underlying Child-Pugh B Cirrhosis—Evidence and Controversy. Oncologist 2009;14(1):67-9.

July 2023 added general statement on hepatitis B testing

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top