Sorafenib: Drug information

(For additional information see "Sorafenib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

NexAVAR

Brand Names: Canada

Nexavar

Pharmacologic Category

Antineoplastic Agent, Tyrosine Kinase Inhibitor; Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor

Dosing: Adult

Note: Interrupt treatment (temporarily) in patients undergoing major surgical procedures.

Hepatocellular cancer (HCC): Oral: 400 mg twice daily; continue until no longer clinically benefiting or until unacceptable toxicity occurs (Llovet 2008)

Renal cell cancer (RCC), advanced: Oral: 400 mg twice daily; continue until no longer clinically benefiting or until unacceptable toxicity occurs (Escudier 2007; Escudier 2009)

Thyroid cancer, differentiated: Oral: 400 mg twice daily; continue until no longer clinically benefiting or until unacceptable toxicity occurs (Brose 2013)

Angiosarcoma (off-label use): Oral: 400 mg twice daily (Maki 2009)

Gastrointestinal stromal tumor (GIST) (off-label use): Oral: 400 mg twice daily (Wiebe 2008)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Manufacturer's labeling: No dosage adjustment is necessary for mild, moderate, or severe impairment (not dependent on dialysis); has not been studied in dialysis patients.

A pharmacokinetic study evaluated sorafenib dosing to determine an initial tolerable dose in patients with varying degrees of renal dysfunction. The following empiric starting doses were identified based on patient tolerance (Miller 2009):

CrCl 40 to 59 mL/minute: 400 mg twice daily

CrCl 20 to 39 mL/minute: 200 mg twice daily

CrCl <20 mL/minute: Data inadequate to define dose

Hemodialysis (any CrCl): 200 mg once daily

Dosing: Hepatic Impairment

Hepatic impairment at baseline:

Manufacturer's labeling:

Mild to moderate (Child-Pugh class A and B) impairment: No dosage adjustment is necessary.

Severe impairment (Child-Pugh class C): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

A pharmacokinetic study evaluated sorafenib dosing to determine an initial tolerable dose in patients with varying degrees of hepatic dysfunction. The following empiric starting doses were identified based on patient tolerance (Miller 2009):

Mild hepatic dysfunction (bilirubin >1 to ≤1.5 times ULN and/or AST >ULN): 400 mg twice daily

Moderate hepatic dysfunction (bilirubin >1.5 to ≤3 times ULN; any AST): 200 mg twice daily

Severe hepatic dysfunction:

Albumin <2.5 g/dL (any bilirubin and any AST): 200 mg once daily

Bilirubin >3 to 10 x ULN (any AST): A dose of 200 mg every 3 days was **not** tolerated, therefore no dosage was identified in this pharmacokinetic study for patients meeting these parameters.

Drug-induced liver injury during treatment: Unexplained (eg, not due to viral hepatitis or progressive underlying malignancy) significantly increased transaminases: Discontinue treatment.

Dosing: Adjustment for Toxicity

Temporary interruption and/or dosage reduction may be necessary for management of adverse drug reactions.

Cardiovascular toxicity:

Cardiac ischemia or infarction: Consider temporary interruption or permanent discontinuation.

Hypertension, severe or persistent (despite antihypertensive therapy): Consider temporary interruption or permanent discontinuation.

QT prolongation (QTc interval >500 msec or ≥60 msec increase from baseline): Interrupt treatment.

Gastrointestinal perforation: Permanently discontinue.

Hemorrhage requiring medical intervention: Consider permanent discontinuation.

Dermatologic toxicity: If Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, discontinue therapy.

US labeling:

RCC and HCC: If dosage reductions are necessary, decrease dose to 400 mg once daily. If further reductions are needed, decrease dose to 400 mg every other day.

Grade 1 (numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet which do not disrupt normal activities): Continue sorafenib and consider symptomatic treatment with topical therapy.

Grade 2 (painful erythema and swelling of the hands or feet and/or discomfort affecting normal activities):

First occurrence: Continue sorafenib and consider symptomatic treatment with topical therapy. **Note:** If no improvement within 7 days, see dosing for second or third occurrence.

Second or third occurrence (or no improvement after 7 days of 1st occurrence): Hold treatment until resolves to grade 0-1; resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day).

Fourth occurrence: Discontinue treatment.

Grade 3 (moist desquamation, ulceration, blistering, or severe pain of the hands or feet or severe discomfort that prevents working or performing daily activities):

First or second occurrence: Hold treatment until resolves to grade 0-1; resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day).

Third occurrence: Discontinue treatment.

Thyroid cancer:

First dose level reduction: Reduce to 600 mg daily (in 2 divided doses, as 400 mg and 200 mg, separated by 12 hours).

Second dose level reduction: Reduce dose to 200 mg twice daily.

Third dose level reduction: Reduce dose to 200 mg once daily.

Grade 1 (numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet which do not disrupt normal activities): Continue sorafenib treatment.

Grade 2 (painful erythema and swelling of the hands or feet and/or discomfort affecting normal activities):

First occurrence: Decrease dose to 600 mg daily (in divided doses). **Note:** If no improvement within 7 days, see dosing for second occurrence.

Second occurrence (or no improvement after 7 days of the reduced dose after 1st occurrence): Hold treatment until resolved or improved to grade 1; if resumed, decrease the dose by 1 dose level.

Third occurrence: Hold treatment until resolved or improved to grade 1; if resumed, decrease the dose by 1 dose level.

Fourth occurrence: Permanently discontinue.

Grade 3 (moist desquamation, ulceration, blistering, or severe pain of the hands or feet or severe discomfort that prevents working or performing daily activities):

First occurrence: Hold treatment until resolved or improved to grade 1; if resumed, decrease by 1 dose level.

Second occurrence: Hold treatment until resolved or improved to grade 1; if resumed, decrease by 2 dose levels.

Third occurrence: Permanently discontinue.

Following improvement of grade 2 or 3 dermatologic toxicity to grade 0 or 1 after at least 28 days of a reduced dose, the sorafenib dose may be increased 1 dose level from the reduced dose (~50% of patients requiring dose reduction for dermatologic toxicity may meet the criteria for increased dosing; and half of those patients may tolerate the increased dose without recurrent grade 2 or higher dermatologic toxicity).

Canadian labeling: RCC and HCC:

Grade 1 (any occurrence): Initiate supportive treatment immediately and continue sorafenib.

Grade 2:

First occurrence: Initiate supportive treatment immediately and consider a dose reduction to 400 mg daily for 28 days. If toxicity resolves to ≤grade 1 after 28 days with dose reduction, increase dose to 400 mg twice daily. If toxicity does not resolve to ≤ grade 1 despite dose reduction, withhold treatment for a minimum of 7 days until toxicity resolves to ≤ grade 1, then resume treatment at reduced dose of 400 mg daily for 28 days. If toxicity remains ≤ grade 1 at the reduced dose for 28 days, increase dose to 400 mg twice daily.

Second or third occurrence: Follow procedure for first occurrence; however, when resuming treatment, decrease dose to 400 mg daily (indefinitely).

Fourth occurrence: Treatment discontinuation should be considered based on clinical assessment and patient preference.

Grade 3:

First occurrence: Initiate supportive measures immediately and withhold treatment for a minimum of 7 days and until toxicity ≤ grade 1. Resume at reduced dose of 400 mg daily for 28 days. If toxicity remains ≤ grade 1 at the reduced dose for 28 days, increase dose to 400 mg twice daily.

Second occurrence: Follow procedure for first occurrence; however, when resuming treatment, decrease dose to 400 mg daily (indefinitely).

Third occurrence: Treatment discontinuation should be considered based on clinical assessment and patient preference.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

NexAVAR: 200 mg

Generic Equivalent Available (US) No

Prescribing and Access Restrictions Available from specialty pharmacies. Further information may be obtained at 1-866-639-2827 or www.nexavar-us.com.

Administration Administer on an empty stomach (1 hour before or 2 hours after eating).

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Hepatocellular cancer: Treatment of unresectable hepatocellular cancer (HCC)

Renal cell cancer, advanced: Treatment of advanced renal cell cancer (RCC)

Thyroid cancer, differentiated: Treatment of locally recurrent or metastatic, progressive, differentiated thyroid cancer (refractory to radioactive iodine treatment)

Use: Off-Label

Angiosarcoma, recurrent or metastatic; Gastrointestinal stromal tumor, resistant

Medication Safety Issues

Sound-alike/look-alike issues:

NexAVAR may be confused with NexIUM

SORAfenib may be confused with axitinib, gefitinib, imatinib, regorafenib, sonidegib, SUNItinib, vandetanib, vemurafenib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Cardiovascular: Hypertension (9% to 41%; grade 3: 3% to 4%; grade 4: <1%; grades 3/4: 10%, onset: ~3 weeks)

Central nervous system: Fatigue (37% to 46%), headache (≤10% to 17%), mouth pain (14%), voice disorder (13%), peripheral sensory neuropathy (≤13%), pain (11%)

Dermatologic: Palmar-plantar erythrodysesthesia (21% to 69%; grade 3: 6% to 8%; grades 3/4: 19%), alopecia (14% to 67%), skin rash (including desquamation; 19% to 40%; grade 3: ≤1%; grades 3/4: 5%), pruritus (14% to 20%), xeroderma (10% to 13%), erythema (≥10%)

Endocrine & metabolic: Hypoalbuminemia (≤59%), weight loss (10% to 49%), hypophosphatemia (35% to 45%; grade 3: 11% to 13%; grade 4: <1%), increased thyroid stimulating hormone level (>0.5 mU/L: 41%; due to impairment of exogenous thyroid suppression), hypocalcemia (12% to 36%), increased amylase (30% to 34% [usually transient])

Gastrointestinal: Diarrhea (43% to 68%; grade 3: 2% to 10%; grade 4: <1%), increased serum lipase (40% to 41% [usually transient]), abdominal pain (11% to 31%), decreased appetite (30%), anorexia (16% to 29%), stomatitis (24%), nausea (21% to 24%), constipation (14% to 16%), vomiting (11% to 16%)

Hematologic & oncologic: Lymphocytopenia (23% to 47%; grades 3/4: ≤13%), thrombocytopenia (12% to 46%; grades 3/4: 1% to 4%), increased INR (≤42%), neutropenia (≤18%; grades 3/4: ≤5%), hemorrhage (15% to 17%; grade 3: 2%), leukopenia

Hepatic: Increased serum ALT (59%; grades 3/4: 4%), increased serum AST (54%; grades 3/4: 2%), hepatic insufficiency (≤11%; grade 3: 2%; grade 4: 1%)

Infection: Infection

Neuromuscular & skeletal: Limb pain (15%), weakness (12%), myalgia

Respiratory: Dyspnea (≤14%), cough (≤13%)

Miscellaneous: Fever (11%)

1% to 10%:

Cardiovascular: Ischemic heart disease (including myocardial infarction; ≤3%), cardiac failure (2%, congestive), flushing

Central nervous system: Depression, glossalgia

Dermatologic: Hyperkeratosis (7%), acne vulgaris, exfoliative dermatitis, folliculitis

Endocrine & metabolic: Hypokalemia (5% to 10%), hyponatremia, hypothyroidism

Gastrointestinal: Dysgeusia (6%), dyspepsia, dysphagia, gastroesophageal reflux disease, mucositis, xerostomia

Genitourinary: Erectile dysfunction, proteinuria

Hematologic & oncologic: Squamous cell carcinoma of skin (3%; grades 3/4: 3%), anemia

Hepatic: Increased serum transaminases (transient)

Neuromuscular & skeletal: Muscle spasm (10%), arthralgia (≤10%), myalgia

Renal: Renal failure

Respiratory: Epistaxis (7%), flu-like symptoms, hoarseness, rhinorrhea

<1%, postmarketing, and/or case reports: Acute renal failure, anaphylaxis, angioedema, aortic dissection, amyotrophy, cardiac arrhythmia, cardiac failure, cerebral hemorrhage, cholangitis, cholecystitis, dehydration, eczema, erythema multiforme, gastritis, gastrointestinal hemorrhage, gastrointestinal perforation, gynecomastia, hepatic failure, hepatitis, hypersensitivity reaction (skin reaction, urticaria), hypertensive crisis, hyperthyroidism, increased serum alkaline phosphatase, increased serum bilirubin, interstitial pulmonary disease (acute respiratory distress, interstitial pneumonia, lung inflammation, pneumonitis, pulmonitis, radiation pneumonitis), jaundice, malignant neoplasm of skin (keratoacanthomas), nephrotic syndrome, ostealgia, osteonecrosis of the jaw, pancreatitis, pleural effusion, prolonged QT interval on ECG, respiratory tract hemorrhage, reversible posterior leukoencephalopathy syndrome, rhabdomyolysis, Stevens-Johnson syndrome, thromboembolism, tinnitus, toxic epidermal necrolysis, transient ischemic attacks, tumor lysis syndrome, tumor pain

Contraindications

Known severe hypersensitivity to sorafenib or any component of the formulation; use in combination with carboplatin and paclitaxel in patients with squamous cell lung cancer

Warnings/Precautions

Concerns related to adverse effects:

• Bleeding: Increased risk of bleeding may occur; consider permanently discontinuing with serious bleeding events (eg, requires medical intervention). Fatal bleeding events have been reported. Thyroid cancer patients with tracheal, bronchial, and esophageal infiltration should be treated with local therapy prior to administering sorafenib due to the potential bleeding risk.

• Cardiac ischemia/infarction: May cause cardiac ischemia or infarction; consider discontinuation (temporary or permanent) in patients who develop these conditions. Use in patients with unstable coronary artery disease or recent myocardial infarction has not been studied.

• Dermatologic toxicity: Hand-foot skin reaction and rash (generally grades 1 or 2) are the most common drug-related adverse events, and typically appear within the first 6 weeks of treatment; usually managed with topical treatment, treatment delays, and/or dose reductions. Consider permanently discontinuing with severe or persistent dermatological toxicities. The risk for hand-foot skin reaction increased with cumulative doses of sorafenib (Azad 2009). Severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported; may be life-threatening. Discontinue sorafenib for suspected SJS or TEN.

The following treatments may be used to manage hand-foot skin reaction in addition to the recommended dosage modifications (Lacouture 2008): Prior to treatment initiation, a pedicure is recommended to remove hyperkeratotic areas/calluses, which may predispose to HFSR; avoid vigorous exercise/activities which may stress hands or feet. During therapy, patients should reduce exposure to hot water (may exacerbate hand-foot symptoms); avoid constrictive footwear and excessive skin friction. Patients may also wear thick cotton gloves or socks and should wear shoes with padded insoles. Grade 1 HFSR may be relieved with moisturizing creams, cotton gloves and socks (at night) and/or keratolytic creams such as urea (20% to 40%) or salicylic acid (6%). Apply topical steroid (eg, clobetasol ointment) twice daily to erythematous areas of grade 2 HFSR; topical anesthetics (eg, lidocaine 2%) and then systemic analgesics (if appropriate) may be used for pain control. Resolution of acute erythema may result in keratotic areas which may be softened with keratolytic agents.

• Gastrointestinal perforation: Gastrointestinal perforation has been reported (rare); monitor patients for signs/symptoms (abdominal pain, constipation, or vomiting); discontinue treatment if gastrointestinal perforation occurs.

• Hypertension: May cause hypertension (generally mild-to-moderate), especially in the first 6 weeks of treatment; monitor. Use caution in patients with underlying or poorly-controlled hypertension. Consider discontinuing (temporary or permanent) in patients who develop severe or persistent hypertension while on appropriate antihypertensive therapy.

• QT prolongation: QT prolongation has been observed; may increase the risk for ventricular arrhythmia. Avoid use in patients with congenital long QT syndrome. Monitor electrolytes and ECG in patients with heart failure, bradyarrhythmias, and concurrent medications know to prolong the QT interval. Correct electrolyte (calcium, magnesium, potassium) imbalances. Interrupt treatment for QTc interval >500 msec or for ≥60 msec increase from baseline.

• Thyroid impairment: Sorafenib impairs exogenous thyroid suppression. TSH level elevations were commonly observed in the thyroid cancer study; monitor TSH levels monthly and as clinically necessary, and adjust thyroid replacement as needed.

• Wound healing complications: May complicate wound healing; temporarily withhold treatment for patients undergoing major surgical procedures. The appropriate timing to resume sorafenib after major surgery has not been determined.

Disease-related concerns:

• Heart failure: In a scientific statement from the American Heart Association, sorafenib has been determined to be an agent that may exacerbate underlying myocardial dysfunction (magnitude: minor) (AHA [Page 2016]).

• Hepatic impairment: Sorafenib levels in patients with mild-to-moderate hepatic impairment (Child-Pugh classes A and B) were similar to levels observed in patients without hepatic impairment. Not studied in patients with severe hepatic impairment (Child-Pugh class C). In a small study of Asian patients with advanced HCC, sorafenib demonstrated efficacy with adequate tolerability in a hepatitis B-endemic area (Yau 2009). There have been reports of sorafenib-induced hepatitis (including hepatic failure and death) which is characterized by hepatocellular liver damage and transaminase increases (significant); increased bilirubin and INR may also occur. Monitor hepatic function regularly; discontinue sorafenib for unexplained significant transaminase increases.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information. Avoid concurrent use with strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St John's wort); may decrease sorafenib levels/effects. Use caution when administering sorafenib with compounds that are metabolized predominantly via UGT1A1 (eg, irinotecan). The incidence of hand-foot skin reaction is increased in patients treated with sorafenib plus bevacizumab in comparison to those treated with sorafenib monotherapy (Azad 2009). Use in combination with carboplatin and paclitaxel in patients with squamous cell lung cancer is contraindicated. Monitor PT/INR in patients on warfarin therapy due to potential for bleeding events to occur.

Metabolism/Transport Effects

Substrate of CYP3A4 (minor), UGT1A9; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP/ABCG2, BSEP/ABCB11, CYP2C8 (weak), CYP2C9 (moderate), UGT1A9

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Acetaminophen: May enhance the hepatotoxic effect of SORAfenib. SORAfenib may increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Amodiaquine: CYP2C8 Inhibitors may increase the serum concentration of Amodiaquine. *Risk X: Avoid combination*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bevacizumab: May enhance the adverse/toxic effect of SORAfenib. Specifically, the risk for hand-foot skin reaction may be increased. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Angiogenesis Inhibitors (Systemic) may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

Bosentan: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Bosentan. Management: Concomitant use of both a CYP2C9 inhibitor and a CYP3A inhibitor or a single agent that inhibits both enzymes with bosentan is likely to cause a large increase in serum concentrations of bosentan and is not recommended. See monograph for details. *Risk C: Monitor therapy*

Cannabis: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Cannabis. More specifically, tetrahydrocannabinol serum concentrations may be increased. *Risk C: Monitor therapy*

CARBOplatin: SORAfenib may enhance the adverse/toxic effect of CARBOplatin. Management: Concurrent sorafenib with carboplatin and paclitaxel in patients with squamous cell lung cancer is contraindicated. Use in other settings is not specifically contraindicated but should be approached with added caution. *Risk X: Avoid combination*

Carvedilol: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Carvedilol.

Specifically, concentrations of the S-carvedilol enantiomer may be increased. *Risk C: Monitor therapy*

Cholic Acid: BSEP/ABCB11 Inhibitors may decrease the excretion of Cholic Acid. *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk with Inhibitors): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of SORAfenib. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of SORAfenib. *Risk C: Monitor therapy*

Dacarbazine: SORAfenib may decrease the serum concentration of Dacarbazine. Sorafenib may also increase the concentration of dacarbazine's active metabolite. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

DOCEtaxel: SORAfenib may increase the serum concentration of DOCEtaxel. *Risk C: Monitor therapy*

DOXOrubicin (Conventional): SORAfenib may increase the serum concentration of DOXOrubicin (Conventional). *Risk C: Monitor therapy*

Dronabinol: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fluorouracil (Systemic): SORAfenib may decrease the serum concentration of Fluorouracil (Systemic). SORAfenib may increase the serum concentration of Fluorouracil (Systemic). *Risk C: Monitor therapy*

Fluorouracil (Topical): SORAfenib may decrease the serum concentration of Fluorouracil (Topical). SORAfenib may increase the serum concentration of Fluorouracil (Topical). *Risk C: Monitor therapy*

Irinotecan Products: SORAfenib may increase serum concentrations of the active metabolite(s) of

Irinotecan Products. Specifically, concentrations of SN-38 may be increased. SORAfenib may increase the serum concentration of Irinotecan Products. *Risk C: Monitor therapy*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

MiFEPRIStone: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying). Management: Though the drugs listed here have uncertain QT-prolonging effects, they all have some possible association with QT prolongation and should generally be avoided when possible. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neomycin: May decrease the serum concentration of SORAfenib. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

PACLitaxel (Conventional): SORAfenib may enhance the adverse/toxic effect of PACLitaxel (Conventional). Management: Concurrent sorafenib with carboplatin and paclitaxel in patients with squamous cell lung cancer is contraindicated. Use in other settings is not specifically contraindicated but should be approached with added caution. *Risk X: Avoid combination*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Propacetamol: SORAfenib may enhance the hepatotoxic effect of Propacetamol. SORAfenib may increase serum concentrations of the active metabolite(s) of Propacetamol. Specifically, acetaminophen exposure may be increased. Management: Consider less frequent and/or lower daily doses of propacetamol in patients who are also taking sorafenib. Monitor for liver toxicity, particularly with higher propacetamol doses. *Risk D: Consider therapy modification*

QTc-Prolonging Agents (Highest Risk): QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) may enhance the QTc-prolonging effect of QTc-Prolonging Agents (Highest Risk). Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

QTc-Prolonging Agents (Moderate Risk): QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) may enhance the QTc-prolonging effect of QTc-Prolonging Agents (Moderate Risk). *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of SORAfenib. *Risk X: Avoid combination*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tetrahydrocannabinol: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Tetrahydrocannabinol. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Warfarin: SORAfenib may enhance the anticoagulant effect of Warfarin. SORAfenib may increase the serum concentration of Warfarin. Management: Warfarin dose adjustment will likely be necessary. Increase frequency of INR monitoring during sorafenib therapy (particularly when starting or stopping therapy), and increase monitoring for signs and symptoms of bleeding. *Risk D: Consider therapy modification*

Food Interactions Bioavailability is decreased 29% with a high-fat meal (bioavailability is similar to fasting state when administered with a moderate-fat meal). Management: Administer on an empty stomach 1 hour before or 2 hours after eating.

Pregnancy Risk Factor D (show table)

Pregnancy Implications Animal reproduction studies have demonstrated teratogenicity and fetal loss. Based on its mechanism of action and because sorafenib inhibits angiogenesis, a critical component of fetal development, adverse effects on pregnancy would be expected. Women of childbearing potential should be advised to avoid pregnancy. Men and women of reproductive potential should use effective birth control during treatment and for at least 2 weeks after treatment is discontinued.

Breast-Feeding Considerations It is not known if sorafenib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, a decision should be made to discontinue

sorafenib or to discontinue breastfeeding during therapy, taking into account the importance of treatment to the mother.

Monitoring Parameters

CBC with differential, electrolytes (magnesium, potassium, calcium), phosphorus, lipase and amylase levels; liver function tests; blood pressure (baseline, weekly for the first 6 weeks, then periodic); monitor for hand-foot skin reaction and other dermatologic toxicities; monitor ECG in patients at risk for prolonged QT interval; signs/symptoms of bleeding, GI perforation, and heart failure.

Thyroid function testing:

Patients with differentiated thyroid cancer: Monitor TSH monthly.

Patients with RCC and HCC (Hamnvik 2011):

Pre-existing levothyroxine therapy: Obtain baseline TSH levels, then monitor every 4 weeks until levels and levothyroxine dose are stable, then monitor every 2 months

Without pre-existing thyroid hormone replacement: TSH at baseline, then every 4 weeks for 4 months, then every 2 to 3 months

Mechanism of Action

Multikinase inhibitor; inhibits tumor growth and angiogenesis by inhibiting intracellular Raf kinases (CRAF, BRAF, and mutant BRAF), and cell surface kinase receptors (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-beta, cKIT, FLT-3, RET, and RET/PTC)

Pharmacodynamics/Kinetics

Protein binding: 99.5%

Metabolism: Hepatic, via CYP3A4 (primarily oxidated to the pyridine N-oxide; active, minor) and UGT1A9 (glucuronidation)

Bioavailability: 38% to 49%; reduced by 29% when administered with a high-fat meal

Half-life elimination: 25 to 48 hours

Time to peak, plasma: ~3 hours

Excretion: Feces (77%, 51% of dose as unchanged drug); urine (19%, as metabolites)

Pricing: US

Tablets (NexAVAR Oral)

200 mg (120): $19775.32

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

Brand Names: International

Neksavar (UA); Nexavar (AE, AR, AT, AU, BE, BG, BR, CH, CL, CN,

CO, CR, CU, CY, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IS, IT, JO, JP, KR, KW, LB, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, SV, TH, TR, TW, UY, VN); Sofenib (BD); Sorafen (BD); Soranib (VN); Soranix (BD)

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