DRUG NAME: Sorafenib

SYNONYM(S): sorafenib tosylate,[1] BAY 43-9006[2]

COMMON TRADE NAME(S): NEXAVAR®

CLASSIFICATION: multikinase inhibitor[1]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Sorafenib inhibits tumour growth by blocking the activity of serine/threonine and receptor tyrosine kinases located in both the tumour cell (c-Raf, b-Raf, V600E b-Raf, KIT, and Flt3) and in the tumour vasculature (c-Raf, VEGFR2, VEGFR3, and PDGFR-beta).[1,3]

PHARMACOKINETICS:

Oral Absorption	relative bioavailability, oral tablet: 38-49%, compared to oral solution bioavailability reduced 29% by a high-fat meal time to peak: 3 h	
Distribution	steady-state achieved within 7 days	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	99.5%
Metabolism	primarily hepatic (CYP3A4, UGT1A9); eight metabolites identified	
	active metabolite(s)	pyridine N-oxide; potency similar to that of sorafenib
	inactive metabolite(s)	unspecified
Excretion	primarily hepatic	
	urine	19% as metabolites
	feces	77%; unchanged drug: 51%
	terminal half life	25-48 h
	clearance	no information found
Ethnicity	Japanese patients showed a 45% lower sorafenib exposure (AUC) as compared to Caucasian patients (limited data); clinical significance unknown.	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Renal cell cancer

Other uses:
Liver cancer[2]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- Avoid use in patients with unstable coronary artery disease or recent myocardial infarction.[4]

- Use with caution in patients with underlying or poorly-controlled hypertension and in patients with cardiac disease.
- Temporary interruption of therapy is recommended in patients undergoing major surgical procedures for precautionary reasons related to wound healing.[1]

Special populations: There is a potential risk to ***children and adolescents*** regarding effects on structure and composition of bone and teeth.[1]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vivo* chromosome test.[1] One intermediate in the manufacturing process, which is also present in the final drug substance (<0.15%), was mutagenic in Ames testing.[1] Sorafenib is clastogenic in mammalian *in vitro* mutation tests.[1]

Fertility: Animal studies indicate that sorafenib may impair male and female fertility.[1]

Pregnancy: FDA Pregnancy Category D.[4] 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). Adequate contraception should be used during therapy and for at least two weeks after completion of therapy.[1]

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

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.[5] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	anemia (1-10%, severe 2%)
	leukopenia (1-10%)
	lymphopenia (23%, severe 13%)[4]
	neutropenia (<18%, severe 5%)[4]
	thrombocytopenia (<12%, severe 1%)[4]
cardiovascular (arrhythmia)	arrhythmia (<1%)
cardiovascular (general)	cardiac failure (<1%)
	cardiac ischemia/infarction (3%)
	hypertension (17%, severe 4%); see paragraph following **Side Effects** table
	hypertensive crisis (<1%)[4]
coagulation	thromboembolism (<1%)[4]
constitutional symptoms	asthenia (1-10%)
	fatigue (33-40%, severe 6%)[1,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pyrexia (1-10%)
	weight loss (1-10%)
dermatology/skin	acne (1-10%)
	actinic keratosis[7]
	alopecia (27%, severe <1%)
	dry skin (11%, severe 0%)
	erythema (>10%)
	erythema multiforme (<1%)[4,8]
	exfoliative dermatitis (1-10%)
	flushing (1-10%)
	hand-foot skin reaction (25-35%, severe 6-8%)[1,6], stump reaction[9]; see paragraph following **Side Effects** table
	hypersensitivity (skin reaction, urticaria) (<1%)[4]
	keratoacanthomas[10]
	pruritis (18%, severe <1%)
	rash/desquamation (27-40%, severe <1%)[1,6]
	yellow skin discolouration[11]
endocrine	hypothyroidism (<1%)[4]
gastrointestinal	*emetogenic potential: rare*
	constipation (15%)[4]
	dehydration (<1%)
	diarrhea (34-43%, severe 2-4%)[1,6]
	dyspepsia (1-10%)
	dysphagia (1-10%)
	gastrointestinal perforation (<1%); see paragraph following **Side Effects** table
	mucositis/stomatitis (including xerostomia and glossodynia) (1-10%)
	vomiting (sorafenib arm 16% vs. placebo arm 12%)
hemorrhage	***cerebral hemorrhage*** (<1%)
	hemorrhage (15%, severe 2%); all sites, including hematoma, epistaxis, mouth, pulmonary, respiratory tract, and GI tract; see paragraph following **Side Effects** table
hepatobiliary/pancreas	jaundice (<1%)[4]
	pancreatitis (<1%)[4,12]
infection	infection (<1%)[4]
metabolic/laboratory	abnormal INR (<1%)[4]
	hyponatremia (<1%)[4]
	hypophosphatemia (45%, severe 13%)
	increased alkaline phosphatase (<1%)[4]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	increased amylase (30%, severe 1%)[4]
	increased bilirubin (<1%)[4]
	increased lipase (41%, severe 12%)
	increases in transaminases (1-10%); transient
musculoskeletal	arthralgia (1-10%)
	myalgia (1-10%)
	osteonecrosis of the jaw[13,14] (<0.1%)
neurology	depression (1-10%)
	posterior leukoencephalopathy syndrome[15]
	sensory neuropathy (13%, severe <1%)
	transient ischemic attack (<1%)
pain	pain (>10%); including mouth, abdominal, headache, bone, and tumour
pulmonary	hoarseness (1-10%)
renal/genitourinary	acute renal failure (<1%)
sexual/reproductive function	erectile dysfunction (1-10%)
syndromes	influenza-like illness (1-10%)
vascular	leukocytoclastic vasculitis[16]

Adapted from standard reference[1] unless specified otherwise.

Gastrointestinal perforation, in some cases, was not associated with apparent intra-abdominal tumour. Therapy should be discontinued in the event of gastrointestinal perforation.[1]

Hand-foot skin reaction and rash are the most common side effects of sorafenib. Rash and hand-foot skin reaction generally appear during the first six weeks of treatment. Dermatologic toxicities are generally easily managed and may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation.[1] Refer to dose modifications for cutaneous toxicity in **Dosage Guidelines**.

Hemorrhage. If any bleeding event necessitates medical intervention, permanent discontinuation of sorafenib should be considered.[1]

Hypertension is usually mild to moderate, occurs early in the course of treatment (especially in the first six weeks[4]), and is amenable to management with standard antihypertensive therapy. In cases of severe or persistent hypertension, or hypertensive crisis despite adequate antihypertensive therapy, permanent discontinuation should be considered. Blood pressure should be monitored on a weekly basis at the beginning of therapy, and regularly thereafter.[1] Hypertension should be treated in accordance with standard medical practice.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan[1]	no effect on sorafenib pharmacokinetics (CYP2D6 substrate)		
docetaxel[1]	exposure to docetaxel increased	unknown	clinical significance unknown
doxorubicin[1]	AUC of doxorubicin increased 21%	unknown	clinical significance unknown
gemcitabine[1]	no effect on sorafenib pharmacokinetics		
grapefruit juice[17]	may increase plasma level of sorafenib	may inhibit CYP3A4 metabolism of sorafenib in the intestinal wall	in view of ketoconazole data (see below), avoidance of grapefruit juice likely not necessary
irinotecan[1]	AUC of irinotecan and its active metabolite SN-38 increased by 26-42% and 67-120% respectively	unknown; possibly UGT1A1 mediated	clinical significance unknown
ketoconazole[1]	no effect on sorafenib pharmacokinetics (CYP3A4 inhibitor)		
midazolam[1]	no effect on sorafenib pharmacokinetics (CYP3A4 substrate)		
omeprazole[1]	no effect on sorafenib pharmacokinetics (CYP2C19 substrate)		
oxaliplatin[1]	no effect on sorafenib pharmacokinetics		
rifampin[1]	combined AUC of sorafenib and its active primary metabolite was decreased	CYP3A4 induction	clinical significance unknown
warfarin[1]	no change in mean INR; infrequent bleeding events or elevations in INR have been reported	CYP2C9 substrate	regularly monitor for bleeding and changes in INR

Sorafenib inhibits glucuronidation by the UGT1A1 and UGT1A9 pathways. Systemic exposure to substrates of UGT1A1 and UGT1A9 may be increased when co-administered with sorafenib. Caution is recommended when administering sorafenib together with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g., irinotecan).[1]

Sorafenib is a major inhibitor of CYP2B6 and CYP2C8. Systemic exposure to substrates of CYP2B6 and CYP2C8 may increase when co-administered with sorafenib.[1,17] Sorafenib is a minor inhibitor of CYP2C19, CYP2D6, and CYP3A4.[1]

Sorafenib is a competitive inhibitor of CYP2C9.[1]

SUPPLY AND STORAGE:

Tablets: Bayer supplies sorafenib as a 200 mg film-coated tablet. Store at room temperature.[1]

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: 400 mg PO twice daily,[1] at least one hour before or two hours after a meal[3]

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: mild to moderate impairment: no adjustment required[1]
severe impairment (CrCl < 30 mL/min): no information found

Dosage in hepatic failure: mild to moderate impairment (Child-Pugh A and B): no adjustment required[1]
severe impairment (Child-Pugh C): no information found

Dosage in dialysis: no information found

Dosage in elderly: no adjustment required

DOSE MODIFICATIONS FOR CUTANEOUS TOXICITY[3]:

NCIC Grade	Description	1st occurrence	2nd occurrence	3rd occurrence	4th occurrence
1	numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of hands or feet not disrupting normal activities	continue; consider topical therapy for symptom relief	continue; consider topical therapy for symptom relief	continue; consider topical therapy for symptom relief	continue; consider topical therapy for symptom relief
2	painful erythema and swelling of hands or feet and/or discomfort affecting normal activities	continue; consider topical therapy for symptom relief; if no improvement in 7 days, treat as 2nd occurrence	interrupt until toxicity resolves to Grade 0 or 1; consider dose reduction*	interrupt until toxicity resolves to Grade 0 or 1; consider dose reduction*	discontinue
3	moist desquamation, ulceration, blistering or severe pain of hands or feet, or severe discomfort causing patient to be unable to work or perform activities of daily living	interrupt until toxicity resolves to Grade 0 or 1; consider dose reduction*	interrupt until toxicity resolves to Grade 0 or 1; consider dose reduction*	discontinue	-

* dose level -1 = 400 mg once daily; dose level -2 = 400 mg every other day[1]

Children:

Oral: safety or effectiveness has not been established

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