National PBM Drug Monograph

Sorafenib (Nexavar®)

July 2006

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Efficacy:

- Sorafenib is a multikinase inhibitor of intracellular kinases and receptor tyrosine kinases that decreases cell proliferation.
- It is metabolized primarily in the liver by CYP3A4 and glucuronidation by UGT1A9 with the majority of the parent drug and metabolite excreted in the feces.
- It has not been studied in patients with severe (Child-Pugh C) hepatic impairment; it has not been studied in patients with severe renal impairment or on dialysis; there is no relationship between renal function and AUC in patients with a creatinine clearance $\geq$ 30 mL/minute.
- FDA approved for treatment of patients with advanced renal cell carcinoma.
- In a phase III double-blinded placebo controlled trial in patients with metastatic renal cell carcinoma who had progressed following 1 prior therapy, sorafenib doubled the Progression-Free Survival (167 days) compared to placebo (84 days) despite a low response rate of 2% based on RECIST criteria.
- Overall survival results are not yet mature, however crossover of placebo patients to active treatment following the interim data analysis will dilute out a survival advantage of sorafenib.
- Preliminary Quality of Life (QoL) data found that sorafenib improved respiratory symptoms and emotional symptoms and did not negatively impact energy level, fatigue, quality of sleep, pain, or weight change. More sorafenib patients were bothered by treatment related side effects.
- 17% of patients in the phase III trial had never received prior therapy for metastatic disease; instead they had received therapy as either neoadjuvant or adjuvant treatment with a nephrectomy.
- Supportive data from a Randomized Discontinuation Trial (RDT) showed that after a 12 week run-in period, patients with stable disease randomized to continue sorafenib had a Progression Free Survival of 24 weeks after randomization versus 6 weeks in the placebo arm.

Safety:

- Skin rashes/desquamation and hand foot syndrome are common and dose limiting (see dose adjustment tables)
- Other common adverse events: hypertension (requiring antihypertensives), diarrhea (requiring drug therapy in 16%), alopecia, mucositis, nausea, bleeding, and sensory neuropathy
- Hypertension generally occurs within the first four weeks of therapy
- Other adverse events occurring less commonly include: leukopenia, anemia, neutropenia, thrombocytopenia
- Laboratory abnormalities include hypophosphatemia (asymptomatic and not requiring discontinuation of therapy) and elevated amylase and lipase (clinical pancreatitis in 3 sorafenib patients)

Cost:

- Sorafenib is given daily at a dose of 400mg twice a day. The daily cost of therapy is $107.57.

Recommendation:

- Sorafenib should be available for use for metastatic renal cell carcinoma based on criteria for use.

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of individual patient situations

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating sorafenib for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Sorafenib is a multi-kinase inhibitor that affects tumor proliferation and angiogenesis. It inhibits members of the Raf family of kinases, cell surface tyrosine kinases, vascular endothelial growth factor receptors (VEGFR), and platelet derived growth factor receptors (PDGFR). Sorafenib is thought to decrease tumor cell proliferation (cytostatic effect) as opposed to affecting tumor cell kill via a cytotoxic effect.

Table #1 Sorafenib Pharmacokinetics

Parameter	Sorafenib
Metabolism	Primarily in the liver; oxidative metabolism mediated by CYP3A4 and glucuronidation mediated by UGT1A9; the main circulating metabolite (the pyridine N-oxide) has *in vitro* potency similar to the parent compound
Elimination	77% excreted in the feces within 14 days, 19% in urine as glucuronidated metabolites
Half-life	25-48 hours for parent
Protein Binding	In vitro plasma protein binding 99.5%
Bioavailability	38-49% compared to oral solution; peak plasma levels in 3 hours; Bioavailability similar in fasting state and with moderate-fat meal; High fat meals reduce bioavailability to 29% compared to fasting state.

Special Populations:
Race: Limited data in Japanese patients (N=6) showed 45% lower systemic exposure compared to small population of Caucasians in pooled phase I data. Significance is unknown.
Pediatric: No pharmacokinetic data
Hepatic Impairment: Pharmacokinetics has not been studied in patients with severe (Child-Pugh C) hepatic impairment. Pharmacokinetic parameters were similar in a small group of patients with mild (Child-Pugh A), moderate (Child-Pugh B) or no hepatic impairment.
Renal Impairment: Pharmacokinetics in patients with severe (CrCl <30 ml/min) renal impairment or on dialysis have not been studied. No relationship was shown between renal function and steady state AUC in patients normal renal function or mild (CrCl >50-80 ml/min) or moderate (CrCl 30-50 ml/min) renal impairment.

FDA Approved Indication(s) and Off-label Uses

Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma.

Current VA National Formulary Alternatives

1. High-dose Interleukin-2
2. Interferon

Dosage and Administration

Sorafenib 400mg (2 X 200mg tablets) twice a day without food (at least 1 hour before or 2 hours after eating). Continue therapy until patient is no longer benefiting or unacceptable toxicity.

Dose Adjustments: Temporary dose interruption and/or dose reduction may be necessary due to adverse events. For skin adverse events, see table below. If dose reduction is necessary, the sorafenib dose may be reduced to 400mg once a day. If further dose reduction is necessary, sorafenib may be give as a 400mg dose every other day.

No dose adjustments are needed for: age, gender, body weight, or Child-Pugh A or B hepatic impairment. Sorafenib has not been studied in patients with Child-Pugh C hepatic impairment or severe renal impairment including patients on dialysis.

Table 2: Dose Modifications for Dermatologic Toxicity

Skin Toxicity Grade	Occurrence	Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which do NOT disrupt ADL's	Any occurrence	Continue sorafenib therapy and consider local therapy for symptom relief
Grade 2: Painful erythema and swelling of the hand or feet and/or discomfort affecting the patient's normal activities	First occurrence	Continue sorafenib therapy and consider topical therapy for symptom relief
	No improvement w/i 7 days or 2nd or 3rd occurrence	Interrupt sorafenib therapy until toxicity resolves to Grade 0 or 1 When resuming therapy, decrease sorafenib by one dose level (400mg once a day or 400mg once every other day)
	4th occurrence	Discontinue sorafenib permanently
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, severe discomfort preventing work or ability to perform ADL's	1st or 2nd occurrence	Interrupt sorafenib therapy until toxicity resolves to Grade 0 or 1 When resuming therapy, decrease sorafenib by one dose level (400mg once a day or 400mg once every other day)
	3rd occurrence	Discontinue sorafenib permanently

Efficacy [3]

1. Phase III Randomized Trial Versus Best Supportive Care

Efficacy Measures

1. Primary Endpoints: Overall Survival (OS) and Progression Free Survival (PFS)
2. Secondary Endpoints: Response Rate (RR) and Safety

Summary of efficacy findings

Inclusion:

- Documented unresectable and/or metastatic renal cell carcinoma, histologically or cytologically documented (rare subtypes like pure papillary cell tumor, mixed tumor with

predominant sarcomatoid cells, Bellini carcinoma, medullary carcinoma, or chromophobe oncolytic tumors were excluded)
- No more than 1 prior systemic therapy for advanced disease (completed at least 30 days but not more than 8 months prior to randomization) during or after which the patient had disease progression; a single chemotherapy agent/regimen, a single immunotherapy agent/regimen, or a single investigational agent/regimen were allowable prior therapies; megestrol or medroxyprogesterone used as a single agent in first-line treatment, was allowed as 1 prior systemic therapy
- At least 1 unidimensional measurable lesion according to RECIST criteria
- Risk rated "intermediate" or "low" according to Motzer score*
- Performance Status 0 or 1 ECOG
- Adequate baseline organ function including amylase and lipase

*Motzer Prognostic Risk Categories for Renal Cell Carcinoma
Low risk= no risk factors
Intermediate risk= 1 or 2 risk factors
High risk= more than 2 risk factors

Risk Factors
1. ECOG Performance Status ≥2
2. High LDH > 1.5 X ULN
3. Low serum hemoglobin (<lower limit of normal)
4. High corrected serum calcium (>10mg/dL)
5. absence of prior nephrectomy for removal of primary tumor

Exclusion:
- Completion of prior therapy less than 30 days or more than 8 months before treatment
- Dysrrthymias requiring antiarrhythmic therapy (excluding beta-blockers or digoxin), symptomatic coronary artery disease or ischemia (myocardial infarction within the last 6 months), or congestive heart failure > New York Heart Association (NYHA) Class II
- Active serious bacterial or fungal infections (≥CTC-AE, from NCI)
- History of HIV infection or chronic hepatitis B or C
- History or presence of metastatic brain or meningeal tumors
- Seizure disorder requiring medications
- History of organ allograft
- Risk level "High" on Motzer criteria
- Known or suspected allergy to investigational drug
- Pregnant or breast-feeding

Demographics: Both groups were balanced in terms of demographics and disease characteristics; there were 5% more females in the sorafenib arm. Prognostic factors and risk groups are evenly distributed

Efficacy
Overall survival has not been measured yet as the data has not matured. Progression free survival (survival from randomization to progression or any cause death) was chosen as a second primary endpoint. The relationship of PFS and overall survival is uncertain in renal cell carcinoma. Analysis of prior trials in renal cell carcinoma did show that response rates have not been found to be predictive of a survival benefit.

Table 3: Outcomes from Phase III trial

Outcome	Placebo	Sorafenib
Median PFS (days) 95%CI P (log rank) Hazard ratio 95%CI for HR	84 78, 91	167 139, 174 <0.000001 0.44 0.35, 0.55
Median TTP (days) 95%CI for TTP (time from randomization to progression or last observation) Logrank p Hazard ration (95%CI for HR	84 81, 91	168 164,181 <0.000001 0.4 0.31, 0.52
Response rate by RECIST criteria Complete response (%) Partial response (%) Stable Disease (%) Progressive Disease (%) Not evaluated (%)	 0 0 55.2 30.3 14.5	 0 2.1 77.9 8.7 11.3

Subgroup Analysis of PFS

- Analysis by sex and age showed consistent benefit of sorafenib over placebo
- Median PFS in males and females was similar, and the HR showed a benefit (0.45) in both sexes
- PFS showed a similar benefit in younger and older patients; PFS in patients older than 65 was 181 days with a HR of 0.34
- The HR was well below 1 for all subgroups except a small group (N=26) who were stage 3
- For prognostic subgroups (Motzer score low vs intermediate and ECOG PS 0 vs 1), sorafenib showed a hazard ratio below 0.5 in all categories. PFS was longer in low risk patients (171 days) versus intermediate risk patients (147 days). The HR in low risk patients was 0.53 and in intermediate risk patients 0.39.

Table 4: Effect of prior therapy

Prior Therapy	N	Med PFS Sorafenib	Med PFS Placebo	HR
IL-2/Interferon	632	164	84	0.47
No IL-2/Interferon	137	172	85	0.35
Prior therapy for metastatic disease	636	169	84	0.43
No prior therapy for metastatic disease	133	132	78	0.56

Quality of Life Data:[4]

- From the Phase III trial, 851 patients had a baseline and at least one Patient-Reported Outcome
- Two validated questionnaires: the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FSKI) and the Functional Assessment of Cancer Therapy-General physical well being scale to measure Health Related Quality of Life (HRQOL)
- Higher scores indicate fewer symptoms or less impact on HRQOL

- The instruments were administered on Day 1 of each cycle and date from the first 5 cycles was analyzed
- Completion rates were >90% for each instrument throughout the cycles
- Kidney Cancer Symptoms: Total FKSI scores did not differ between placebo and sorafenib patients in the first five treatments (p=0.98)
- Total FSKI scores and 11 individual scores at baseline correlated with overall survival
- Respiratory symptoms (cough, shortness of breath), emotional symptoms (less worry about their condition, bothered by fevers), and HRQOL symptoms (able to enjoy life) improved on sorafenib
- Sorafenib did not impact energy level, fatigue, quality of sleep, pain, or weight change
- More sorafenib patients commented on bothersome treatment related side effects compared to placebo
- FACT-G Physical Well Being questionnaire showed no difference in mean scores between placebo and sorafenib
- More patients in the sorafenib group rated HRQOL responses as the same or better than in the placebo group (57% vs 37%)
- Patients on sorafenib demonstrated a longer time to health status deterioration versus placebo.

2. Phase II Randomized Discontinuation Trial[5]

Efficacy Measures

Primary Endpoint: Percentage of patients progression free at 12 weeks following random assignment (24 weeks from study entry)

Secondary Endpoints:
Progression Free Survival (PFS) after randomization
Overall PFS from start of treatment
Tumor Response Rate
Safety

Summary of efficacy findings

- 202 patients entered the 12 week run-in phase; 93% completed the run-in
- 73 patients had tumor shrinkage ≥25% from baseline, 34% had tumor measurements ±25% from baseline (stable disease), and 25% showed tumor growth ≥25% or other signs of progression
- Patients with Stable Disease were randomized to either placebo (n=33) or sorafenib (n=32) for 12 weeks
- Patients with progressive disease were discontinued from therapy
- Patients with tumor shrinkage ≥25% continued on open label sorafenib
- The percent of patients progressive free at 12 weeks after randomization was: 18% in the placebo group and 50% in the sorafenib group (p=0.0077)
- Median PFS from the 12 week randomization point was 24 weeks in the sorafenib group and 6 weeks in the placebo group (p=0.0087)
- PFS from start of treatment for patients on sorafenib for 24 weeks was 40 weeks (38 weeks in those with shrinkage 25-50% of baseline value and 47 weeks in those with shrinkage >50% of baseline)
- Overall PFS for the entire population was 29 weeks
- Most common adverse events: fatigue, rash/desquamation, hand-foot skin reactions, pain, diarrhea. The majority were grade 1 or 2.
- Most common grade 3 or 4 adverse event: hypertension in 31%

- Nine patients discontinued therapy because of adverse events

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 16).

Adverse Events (Safety Data)[6,7]

Table 5: Adverse Events Occurring in At Least 10% of Patients

Adverse Events NCI Common Toxicity Criteria	Sorafenib			Placebo		
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %
Any Event	95	31	7	86	22	6
Cardiovascular						
Hypertension	17	3	<1	2	<1	0
Constitutional						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage-all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Abdomen	11	2	0	9	2	0
Joint	10	2	0	6	<1	0
Headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1
Cough	13	<1	0	14	<1	0

Deaths and Other Serious Adverse Events (optional)

Table 6: Serious Adverse Events

Event	Sorafenib %	Placebo %
Death w/I 30 days of receiving study drug	6.5	4.7
Any Serious Event	23.7	17.7
Blood/Bone Marrow		
Decreased Hemoglobin	1.0	2.3
Cardiac		
Ischemia/Infarction	1.0	0.5
Constitutional		
Fatigue	1.0	0.8
Gastrointestinal		
Constipation	1.0	0

Musculoskeletal		
Fracture	1.0	0.8
Other	0.8	1.0
Neurology		
Other	0.8	1.0
Tumor pain	1.6	0.8
Abdominal pain	1.0	0.3
Pulmonary		
Pleural effusion	1.0	0.8
Other	0.5	1.0
Pneumonitis	1.0	0.3
Dyspnea	1.0	1.0

Common Adverse Events

Table 7: Treatment Emergent Adverse Events in 10% or more of patients

Event	Sorafenib %	Placebo %
Any	84.6	73.7
Cardiovascular- Hypertension	10.7	0.8
Constitutional- Fatigue	26.3	23.4
Dermatology		
Rash, desquamation	33.6	13.3
Hand-foot reaction	26.8	4.7
Alopecia	22.9	3.1
Pruritus	16.9	4.4
Gastrointestinal		
Diarrhea	32.8	9.9
Nausea	17.7	14.8
Anorexia	12.2	9.6
Constipation	11.7	7.6
Vomiting	11.2	8.6
Hemorrhage- all sites	11.7	5.2
Neurology- sensory neuropathy	10.2	3.6
Pulmonary- Cough	9.1	10.9

1. Treatment emergent cardiovascular medications were given to 43% of placebo and 49% of sorafenib patients.
2. Treatment emergent anti-diarrheal medicine was given to 5% of placebo and 16% of sorafenib patients
3. Mean weight loss of 2.2 kg in the sorafenib patients and mean weight gain of 0.34 kg in the placebo patients by the end of cycle 4.
4. Oral mucositis was infrequent but more common in the sorafenib group (7.3% vs 0.5% in placebo).

Other Adverse Events

The following were reported in patients taking sorafenib as monotherapy during multiple clinical trials (very common=≥10%, common 1 to less than 10%, uncommon 0.1% to less than 1%.

Cardiovascular: *Uncommon*: hypertensive crisis; myocardial ischemia and/or infarction
Dermatologic: *Very common*: erythema; *Common*: exfoliative dermatitis, acne, flushing; *Uncommon*: folliculitis, eczema, erythema multiforme
Digestive: *Very common*: increased lipase, increased amylase *Common*: mucositis, stomatitis (includes dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon*: pancreatitis, gastrointestinal reflux, gastritis
General: *Very common*: asthenia, pain (includes mouth pain, bone pain, muscle pain) *Common*: decreased appetite, flu-like illness, pyrexia *Uncommon*: infection

Hematologic: *Very common*: leukopenia, lymphopenia *Common*: anemia, neutropenia, thrombocytopenia *Uncommon*: abnormal INR
Hypersensitivity: *Uncommon*: hypersensitivity reactions (skin reactions and urticaria included)
Metabolic: *Very common*: hypophosphatemia *Common*: transient increased in transaminases *Uncommon*: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (includes jaundice), hypothyroidism
Musculoskeletal: *Common*: arthralgia, myalgia
Nervous system: *Common*: depression *Uncommon*: tinnitus
Reproductive: *Common*: erectile dysfunction *Uncommon*: gynecomastia
Respiratory: *Common*: hoarseness *Uncommon*: rhinorrhea

Tolerability

Table 8: Discontinuation

Reason for discontinuing double-blind treatment	Sorafenib %	Placebo %
Adverse event	3.4	3.4
Non-compliant with study medication	0.0	0.4
Consent withdrawn	2.1	3.1
Lost to follow-up	0.7	1.8
Death	4.9	1.3
Missing	2.1	0.4

Skin rashes and hand-foot syndrome are common and are dose limiting.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 16).

Precautions/Contraindications

Precautions

1. Pregnancy Category D: Sorafenib should be assumed to cause fetal harm. There are no adequate and well-controlled studies in pregnant women.
2. Dermatologic Toxicity: Hand-foot reactions are the most common adverse event, are usually Grade 1 or 2 and generally start within the first six weeks of treatment. Management includes topical symptomatic treatment, temporary interruption of therapy, or dose reduction (see Dosing).
3. Hypertension: Treatment related hypertension was reported in 16.9% of sorafenib patients, was generally mild to moderated, started early in the course of treatment, and was managed with standard antihypertensives. Blood pressure should be monitored weekly during the first 6 weeks of sorafenib therapy, then monitored and treated if necessary according to standard practice. If hypertension is severe or persists despite antihypertensive therapy, temporary or permanent discontinuation of sorafenib should be considered.
4. Hemorrhage: Bleeding, regardless of cause, was seen in 15.3% of sorafenib patients versus 8.2% of placebo treated patients. Grade 3 hemorrhage was seen in 2% of sorafenib patients; there were no reports of Grade 4 hemorrhage. If bleeding required intervention, permanent discontinuation of sorafenib should be considered.
5. Cardiac ischemia/infarction: Treatment-emergent cardiac ischemia or infarction was observed in 2.9% of sorafenib patients versus 0.4% of placebo patients. Patients with coronary artery disease or recent infarction were excluded from the study. Consider temporary or permanent discontinuation of sorafenib in patients developing cardiac ischemia or infarction.

6. Race: Pharmacokinetic data from a very limited number of Japanese patients (n=6) showed a 45% lower systemic exposure rate compared to pooled data from Caucasian patients. The clinical significance is unknown.
7. Warfarin co-administration: Infrequent bleeding events or elevations in the INR during concomitant warfarin and sorafenib therapy have been reported. Changes in INR, prothrombin time or episodes of bleeding should be monitored carefully during concomitant therapy.
8. Wound-healing complications: No formal studies have been done. In patients undergoing major surgical procedures, temporary interruption of sorafenib is recommended. There is limited clinical information on when to best restart therapy after the surgical procedure. Restarting should be based in clinical judgment based on adequate wound healing.

Contraindications

Patients with known hypersensitivity reaction to sorafenib or any of its components.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
LA/SA for generic name Sorafenib: Solifenacin, sorine, soriatane, erlotinib, imatinib, Lorabid
LA/SA for trade name Nexavar: Nexium, Nicolar, Temodar, Anabar, Benicar, Cozaar, Donnamar, Niacor, Tasmar, Elspar, Gemzar, Toposar

Drug Interactions

Drug-Drug Interactions

CYP3A4 Inhibitors: Ketoconazole, a potent CYP3A4 inhibitor, administered daily for 7 days did not alter the single dose AUC of sorafenib.

CYP isoform-selective substrates: *In vitro* studies found sorafenib is an inhibitor of CYP2C19, CYP2D6, and CYP3A4. Administration of sorafenib for 28 days did not alter the metabolism of concomitant midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate).

CYP2C9 substrates-Warfarin: The effect of sorafenib on warfarin pharmacokinetics was evaluated indirectly by PT and INR values. Mean changes from baseline in PT and INR did not differ in sorafenib treated patients versus placebo treated patients.

CYP3A4 Inducers: There is no clinical information on the effect of CYP3A4 inducers on sorafenib pharmacokinetics. CYP3A4 inducers (for example carbamazepine, rifampin, St. John's Wort) are expected to increase the metabolism and decrease the plasma levels of sorafenib.

Combination with antineoplastic drugs: Sorafenib had no effect on gemcitabine or oxaliplatin pharmacokinetics in vivo. Concomitant therapy with doxorubicin resulted in a 21% increase in the AUC of doxorubicin. SN-38, the active metabolite of irinotecan is further metabolized by UGT1A1. Concomitant administration with sorafenib resulted in a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. The clinical significance is unknown.

Other In vitro studies: Sorafenib inhibits CYP2B6 and CYP2C8 in vitro and is expected to increase systemic exposure of substrates metabolized by these enzymes.

Sorafenib inhibits glucuronidation by UGT1A1 and UGT1A9 pathways; systemic exposure to substrates for these pathways may be increased with concomitant sorafenib therapy.

CYP inducers: CYP1A2 and 3A4 activity was not altered by in vitro culture with sorafenib.

Drug-Lab Interactions

1. Hypophosphatemia was common in clinical trials and observed in 45% of sorafenib patients compared to 11% in placebo treated patients. Grade 3 hypophosphatemia was seen in 13% of sorafenib patients (3% in placebo patients) but there were no cases of Grade 4 hypophosphatemia in either group.

2. Elevated lipase was found in 41% of sorafenib patients and 30% of placebo patients. Grade 3 or 4 elevations were seen in 12% of sorafenib patients versus 7% of placebo patients. Elevated amylase was seen in 30% of sorafenib patients and 23% of placebo patients. Many of the lipase and amylase increases were transient and did not interrupt therapy. Clinical pancreatitis was seen in 3 of 451 sorafenib patients (two were Grade 4) and 1 of 451 placebo patients.

3. Lymphopenia was seen in 23% of sorafenib patients versus 13% of placebo patients. Grade 3 or 4 lymphopenia was seen in 13% of sorafenib patients and 7% of placebo patients. Neutropenia was observed in 18% of sorafenib and 10% of placebo patients, respectively. Grade 3 or 4 neutropenia was seen in 5% of sorafenib and 2% of placebo patients.

4. Anemia was seen in 44% of sorafenib patients and 49% of placebo patients. Grade 3 or 4 anemia was observed in 2% of sorafenib and 4% of placebo patients.

5. Thrombocytopenia was observed in 12% of sorafenib and 5% of placebo patients. Grade 3 or 4 thrombocytopenia was seen in 1% of sorafenib patients and 0% of placebo patients.

Acquisition Costs

Table 9: Therapy Costs

Drug	Dose	Cost/Day/patient ($)	Cost/30 days/patient ($)
Sorafenib	400 mg twice a day	107.57	3227.22
Interleukin-2 490.21/vial	600,000 IU/kg every 8 hours by 15 minute infusion for a max of 14 doses; an ICU facility and specialist skilled in cardiopulmonary or ICU medicine is required	2941.26	13,725.88/lifetime plus inpatient and intensive care costs.

Pharmacoeconomic Analysis

There are no published pharmacoeconomic research studies involving sorafenib. The manufacturer has provided a cost effectiveness model with an endpoint of incremental cost per life year gained utilizing a Markov model data from sorafenib clinical trials and unpublished data of key clinical studies of comparators.

Conclusions

Efficacy: Sorafenib therapy produces prolongation of Progression-Free Survival in patients with metastatic renal cell carcinoma, either as initial therapy or as second-line therapy following 1 prior therapy for advanced disease. It is the only drug approved for renal cell carcinoma based on a progression-free survival advantage. Overall survival results from the phase III trial are not yet matured, but may be diluted because of crossover allowed from placebo treated patients after the interim analysis of data was completed. A randomized discontinuation trial also supports an advantage in progression-free survival versus placebo. Preliminary QoL data demonstrates that sorafenib improves respiratory symptoms and some emotional symptoms, and does not negatively impact energy level, fatigue, sleep, pain, or weight changes. It did not negatively affect overall Health Related Quality of Life.

Safety: Skin rashes/desquamation and hand-foot syndrome (blistering, pain, redness) are common and are dose limiting. Hypertension is class effect of VEGF inhibitors, occurs in 10% of sorafenib patients, and requires antihypertensive treatment in some patients. Bleeding (not thromboembolism) was more common in the sorafenib group and may preferentially involve mucosal sites. Adverse event in which rates differed between the sorafenib and placebo patients includes hypertension, diarrhea (requiring therapy in some patients), mucositis, sensory neuropathy, and dermatologic affects.

Hypophosphatemia was the most common laboratory abnormality observed in 41% of sorafenib patients. It did not correlate with rates of diarrhea. There were no manifestations of severe phosphate deficiency and it did not lead to discontinuation of the drug. The etiology is unknown and treatment should be based on risk assessment of the patient. Elevated lipase and amylase also did not result in interruption of therapy.

Cost: The cost of drug therapy for 5 months of sorafenib is similar to the cost of interleukin-2 for the drug alone; the IL-2 would also require hospitalization, possible intensive care unit costs, and drug therapy for toxicities.

Recommendations and Place in Therapy[8,9]

Place in Therapy: Patients with renal cell carcinoma (RCC) can present with relapsed disease following nephrectomy, and approximately 30-40% present with metastatic disease that is incurable with surgery. Renal cell carcinoma has been shown to be resistant to standard cytotoxic chemotherapy drugs.

Immunotherapy with interleukin-2 and/or interferon alpha has produced response rates in the 5-20% range, a small percentage of which have been durable (primarily young patients with a high performance status). Until the approval of sorafenib, high-dose Interleukin-2 was the only drug approved for treatment of advanced renal cell carcinoma and its approval was based on the results of phase II trials. It produces substantial toxicities, requires hospitalization and possible intensive

care unit admission, and is not suitable for patients with co-morbidities. It has not been compared to any other therapy. A Cochrane review of immunotherapy for renal cell carcinoma found that response rates did not correlate to survival, thus response rates were not good surrogates for survival. In addition, in the natural history of the disease, there have been rare reports of spontaneous remissions in the placebo arms (7%).[10]

Sorafenib therapy following one prior therapy for metastatic disease doubled the Progression Free Survival time compared to placebo and is the only drug approved for renal cell carcinoma based on improvement in PFS. In addition, 17% of patients in the phase III trial did not receive prior therapy for metastatic disease (prior therapy included neoadjuvant and adjuvant therapies) which helped with the decision by the FDA to not require prior immunotherapy, before being eligible for sorafenib. Toxicities were generally grade 1-3 and were manageable by interrupting therapy and dose reduction.

Inclusion Criteria:

Sorafenib is one choice for first-line therapy of advanced renal cell carcinoma in patients whose disease is unresectable. It is also appropriate as a second-line agent in patients who have progressed following 1 prior therapy for metastatic disease.

1. Other criteria for use of sorafenib include adequate baseline organ function (e.g. CrCl ≥30 mL/min, ALT and AST < 2.5 times ULN, and bilirubin < 1.5 times ULN) and
2. Evaluable disease (Either measurable disease or number of metastatic sites or evaluable symptoms).

Exclusion Criteria:

1. Symptomatic coronary artery disease or ischemia
2. Brain metastases, meningeal metastases
3. Child-Pugh C Hepatic Impairment

Discontinuation:

Sorafenib therapy should be discontinued when there is evidence of disease progression: new metastatic sites, progression of symptoms, increase in measurable tumor size greater than 25% OR intolerable toxicity.

Recommendation: Sorafenib should be available for use in treating patients with advanced or metastatic renal cell carcinoma according to criteria for use.

References

[1] Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Research 2004; 64: 7099-7109.

[2] Beerman M, Patnaik A, Rowinsky EK. Raf: a strategic target for therapeutic development against cancer. J Clin Onc 2005; 23: 6771-6790.

[3] Center for Drug Evaluation and Research Approval Package for: Application Number NDA 21-923. Medical Review found at: http://www.fda.gov/cder/foi/nda/2005/021923_s000_Nexavar_MedR.pdf

[4] Dhanda R, Gondek K, Dong J, Cella D, Bukowski R, Escudier B. A comparison of quality of life and symptoms in kidney cancer patients receiving sorafenib versus placebo. 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 4534

[5] Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24:2505-2512.

[6] Nexavar® Product Package Insert. Bayer Pharmaceuticals Corporation, West Haven, CT. December 2005.

[7] Strumberg D, Awada A. Hirte H, Clark JW, Seeber S, Piccart P, et al. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: is rash associated with treatment outcome? European J Cancer 2006; 42: 548-556.

[8] Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. The Cochrane Database of Systematic Reviews 2006; 1.

[9] Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. J Urology 2000;163:408-417.

[10] Oliver RTD, Nethersell ABW, Bottomly JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. British J Urology 1989;63:128-131.

Prepared April 2006. Contact person: Mark C. Geraci, Pharm.D.

Appendix: Clinical Trials

Include a brief description of the methods used to perform the literature search (database, period, search strategy), inclusion criteria for studies, and sources of any other pertinent information on clinical trials (e.g., review of reference lists, manufacturer's formulary and AMCP dossier, medical reviews and transcripts on FDA Web site; conference abstracts—last resort if information is lacking or abstract is of major importance, etc.) This paragraph is optional. For example:

A literature search was performed on PubMed/Medline (1966 to August 2004) using the search terms <generic name> and <trade name>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Insert text here.

A summary of relevant clinical trials is presented in this section utilizing the example chart formats below. Randomized, placebo-controlled, blinded trials (Grade A evidence) should be reviewed in detail. If available, head-to-head trials against formulary or standard treatments are desired. Trials of low evidence (i.e. open-label, non-comparative, abstract form) should be mentioned with brief synopsis without going into great detail. For reviews including multiple trials a table or chart outlining level of evidence, results of primary efficacy measures and safety data is recommended for easier visual comparison.

<table>
<tr><th>Citation
Design
Analysis type
Setting</th><th>Eligibility Criteria</th><th>Interventions</th><th>Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th><th>Author's conclusions (optional)

Critique (optional)</th></tr>
<tr>
<td>CDER Medical Rev
2006
Phase III, DB,R, MC</td>
<td>Inclusion criteria
1. unresectable a/o metastatic measurable renal cell carcinoma (clear cell)
2. NMT 1 prior systemic therapy with progression during or after
3. At least 1 unidimensional measurable lesion
4. Intermediate or low Motzer score
5. PS 0-1 ECOG
6. adequate baseline organ function including amylase and lipase <1.5 x ULN

Exclusion criteria
1. Rare histologic subtypes
2. Cardiac arrhythmias requiring drug therapy except beta-blockers or digoxin
2. Symptomatic CAD or ischemia (MI w/I last 6</td>
<td>Sorafenib 400mg twice a day (total daily dose = 800mg) plus BSC

Vs

BSC

Primary Endpoints:
1. Overall survival (OS)
2. Progression Free Survival (PFS)</td>
<td>Placebo (N=385) / Sorafenib (N=384)

Male 74.5% / 69.5%
White 72.2 / 71.9
Age median 59 / 58
≥65 y.o. 26.8 / 33.1
ECOG 0 46.8 / 47.9
ECOG 1 52.2 / 49.7
Motzer low 50.4 / 52.1
Intermediate 49.6 / 47.9
Clear Cell 98.7 / 98.2

Prior Therapy
Palliative 79 / 82
Adjuvant 20.7 / 16.9
Neoadjuvant 1.3 / 0.5
No palliative 19 / 15.6</td>
<td>N_R = 769

<table>
<tr><th>Outcome</th><th>PCB</th><th>Sorafenib</th></tr>
<tr><td>PFS
Median (days)
95%CI
P
HR
95%CI</td><td>
84
78,91

</td><td>
167
139,174
<0.000001
0.44
0.35, 0.55</td></tr>
<tr><td>TTP
Median (days)
95%CI
P
HR
95%CI</td><td>
84
81,91

</td><td>
168
164,181
<0.000001
0.4
0.31,0.52</td></tr>
<tr><td>RR (%)
CR
PR
SD
PD</td><td>
0
0
55.2
30.3</td><td>
0
2.1
77.9
8.7</td></tr>
</table>
Overall survival data is not sufficiently mature due to a small number of events.</td>
<td>Tolerability:
Discontinuation due to:
<table>
<tr><td></td><td>PCB</td><td>Sor</td></tr>
<tr><td>AE</td><td>6.2%</td><td>9%</td></tr>
<tr><td>Non-compliant</td><td>0.4</td><td>0</td></tr>
<tr><td>Lost to f/u</td><td>1.8</td><td>0.7</td></tr>
<tr><td>Consent Withdrawn</td><td>3.1</td><td>2.1</td></tr>
</table>
Death (within 30 days if study medications): 23 sorafenib and 18 placebo patients

Over 70% of deaths in both groups due to progressive disease

Serious AE
<table>
<tr><th>AE</th><th>Placebo</th><th>Sorafenib</th></tr>
<tr><td>Any</td><td>17.7%</td><td>23.7%</td></tr>
<tr><td>Decreased Hgb</td><td>2.3</td><td>1.0</td></tr>
<tr><td>Cardiac Ischemia/ Infarction</td><td>0.5</td><td>1.0</td></tr>
<tr><td>Death not assoc wi CTC term or PD</td><td>1.3</td><td>1.0</td></tr>
<tr><td>Fatigue</td><td>0.8</td><td>1.0</td></tr>
<tr><td>Constitutional Other</td><td>1.3</td><td>2.1</td></tr>
<tr><td>Constipation</td><td>0</td><td>1.0</td></tr>
<tr><td>Fracture</td><td>0.8</td><td>1.0</td></tr>
<tr><td>Other Musculo-skeletal</td><td>1.0</td><td>0.3</td></tr>
<tr><td>Neuro</td><td>1.0</td><td>0.8</td></tr>
<tr><td>Pain, tumor</td><td>0.8</td><td>1.6</td></tr>
<tr><td>Pain, abdom</td><td>0.3</td><td>1.0</td></tr>
<tr><td>Pleural effusion</td><td>0.8</td><td>1.0</td></tr>
<tr><td>Pulm other</td><td>1.0</td><td>0.5</td></tr>
<tr><td>Pneumonitis</td><td>0.3</td><td>1.0</td></tr>
<tr><td>Dyspnea</td><td>1.0</td><td>1.0</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
Common AE's in 10% or more
<table>
<tr><td></td><td>Placebo (%)</td><td>Sorafenib(%)</td></tr>
<tr><td>Any</td><td>73.7</td><td>84.6</td></tr>
<tr><td>Cardio</td><td></td><td></td></tr>
</table></td>
<td>23% (177) had at least 1 protocol deviation; 149 were due to inclusion and exclusion criteria; 37 used local laboratories instead of designated labs, and 36 continued double-blinded treatment after documentation of progressive disease.

After analysis of the PFS data by the FDA, accrual was stopped and sorafenib was offered to placebo patients. This crossover may dilute the overall survival results.</td>
</tr>
</table>

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions (optional) *Critique* (optional)
	months) 3. CHF >NYHA Class II 4. Known h/o HIV or chronic Hep B or C 5. Metastatic brain or meningeal tumors 6. Seizure disorder requiring medications 7. High risk based on Motzer score					

Hypertension	0.8	10.7
Constitutional Fatigue	23.4	26.3
Dermatologic Rash/desquam Hand-foot syn Alopecia Pruritis	 13.3 4.7 3.1 4.4	 33.6 26.8 22.9 16.9
GI Diarrhea Nausea Anorexia Constipation Vomiting	 9.9 14.8 9.6 7.6 8.6	 32.8 17.7 12.2 11.7 11.2
Hemorrhage- all	 5.2	 11.7
Neuropathy Sensory	 3.6	 10.2
Cough	10.9	9.1

Summary AE, grades 1-4, at ≥5% for Sorafenib

AE Category	Placebo (%)	Sorafenib (%)
Cardio Hypertension	 0.8	 10.7
Dermatology Rash/desq Hand-foot Alopecia Pruritis	 13.3 4.7 3.1 4.4	 33.6 26.8 22.9 16.9
GI Mucositis,oral Diarrhea Nausea Anorexia Constipation Vomiting	 0.5 9.9 14.8 9.6 7.6 8.6	 7.3 32.8 17.7 12.2 11.7 11.2
Hemorrhage All sites	 5.2	 11.7
Neuropathy Sensory	 3.6	 10.2

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions (optional) *Critique* (optional)

Cough	10.9	9.1

Lab abnormalities in ≥2%

	Placebo		Sorafenib	
Lab	Gr 3	Gr 4	Gr 3	Gr 4
Blood				
Neutro	1.2	0.6	2.7	2.4
Hgb	2.4	0.3	0.9	0.0
Lymphs	5.1	0.6	8.0	0.6
Coags	6.3	0.0	5.0	0.0
Metabolic				
↑amylase	2.4	0.6	1.2	0.0
↑ glucose	4.1	0.3	2.6	0.3
↑ K	2.1	0.6	2.6	0.9
↑ lipase	3.5	1.8	9.3	0.6
↓ Na	3.5	0.0	4.4	0.6
↓ PO_4	1.8	0.0	10.8	0.0

Single-dose studies of QTc interval prolongation: No increase compared to baseline; not routinely measured in phase 1-3 trials. No treatment emergent QTc >500 msec or v-tach.

<table>
<tr><th>Citation
Design
Analysis type
Setting</th><th>Eligibility Criteria</th><th>Interventions</th><th>Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th><th>Author's conclusions (optional)

Critique (optional)</th></tr>
<tr>
<td>Ratain, et al. 2006
Phase 2, R discontinuation study of sorafenib in patients with advanced refractory solid tumors</td>
<td>Inclusion:
1. Advanced RCC
2. ECOG 0 or 1
3. Adequate organ function

Exclusion:
1. Serious arrhythmias
2. CHF NYHAC 3 or 4
3. Active CAD or ischemia
4. Active infection
5. HIV infections
6. Metastatic brain or meningeal tumors unless >6 months from definitive therapy and clinically stable
7. Receiving medication for seizures
8. H/o organ allograft
9. Previous h/o concurrent cancer
10. Surgery w/l previous 4 weeks</td>
<td>Induction:
Sorafenib 400mg twice a day for 12 weeks

Patients with stable disease were randomized to sorafenib or placebo

Patients with tumor shrinkage >25% continued sorafenib in open-label phase

Patients with disease progression (≥25% tumor growth or other evidence of progression) were discontinued from study

Primary outcome:
PFS at 12 weeks after randomization

Secondary:
PFS
TTP
RR
Overall PFS</td>
<td>N=202
Male=74%
Caucasian=90%
Mean age=57.8yr
Previous therapy=82%
MSKCC risk scores:
Low-34%
Intermed=60%
High=3%
Missing=3%</td>
<td>
<table>
<tr><th colspan="2">Patient Disposition</th></tr>
<tr><td>Completed 12 week run-in</td><td>93%</td></tr>
<tr><td>Stable Disease (±24% of baseline)</td><td>Placebo (n=33)
Sorafenib (n=32)</td></tr>
<tr><td>Progressive Disease at 12 weeks</td><td>Discontinue treatment (n=43)</td></tr>
<tr><td>Response (≥25% shrinkage)</td><td>Open label sorafenib (n=79)</td></tr>
</table>
<table>
<tr><th>Outcome</th><th>Placebo</th><th>Sorafenib</th></tr>
<tr><td>PFS 12 weeks after randomiza-tion (24 weeks from study entry)</td><td>18% (6/33)</td><td>50% (16/32)
P=0.0077</td></tr>
<tr><td>Med PFS After ran-domization</td><td>6 weeks</td><td>24 weeks
P=0.0087</td></tr>
<tr><td>Median time to end of treatment for placebo pts with PD who restarted sorafenib</td><td>24 weeks</td><td>N/A</td></tr>
<tr><td>Overall PFS
For pts w/ initial Response</td><td>N/A</td><td>40 weeks (no difference if response 25-50% shrinkage versus >50%</td></tr>
</table>
</td>
<td>Most common treatment related:
Fatigue (73%), rash/desquamation (66%), hand-foot skin reaction (62%), pain (58%), diarrhea (58%).
The majority of adverse events were grade 1 or 2. Nine patients discontinued therapy due to drug toxicity.

Most common grade 3 or 4:
Hypertension (31%)- therapy initiated in 46%</td>
<td></td>
</tr>
</table>

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions (optional) *Critique* (optional)
				shrinkage 38 vs 47 weeks) Overall PFS for entire population from baseline: 29 weeks		

N_R, Number randomized;DB=double-blinded; R=randomized; MC=multicenter; NMT=not more than; ULN=upper limits of normal; PS=performance status; CAD=coronary artery disease; MI=myocardial infarction; CHF=congestive heart failure; NYHA=New York Heart Association; BSC=best supportive care; PFS=progression-free survival (time of randomization until progression or death from any cause); HR=hazard ratio; TTP=time to progression (time from randomization to progression or last observation); RR=response rate; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease