Sorafenib in Differentiated Thyroid Carcinoma

National Drug Monograph Addendum

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum provides information on the use of sorafenib for the treatment of patients with locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment. The original drug monograph can be found at:

https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Drug%20Monographs/Sorafenib,%20Monograph.doc

Introduction[1]

Sorafenib received initial FDA approval in 2005 for the treatment of advanced renal cell carcinoma. The indication for treatment of unresectable hepatocellular carcinoma followed in 2007. This latest indication in DTC, was approved in November, 2013.

Background

Purpose for review

Recent FDA approval.

Issues to be determined:
Does sorafenib offer advantages over current VANF agents?
What safety issues need to be considered?

Other therapeutic options

Key: ORR overall response rate, OS overall survival, P2 phase 2, PFS progression-free survival, PR partial response, SD stable disease, TTP time to progression

Formulary Alternatives	Other Considerations
doxorubicin	Only FDA-approved cytotoxic agent; ORR 25% (all PR) as monotherapy; transient effect; no OS benefit; very limited role Intravenous therapy
Non-formulary Alternative (if applicable)	**Other Considerations**
Vandetanib	FDA-approved for medullary thyroid cancer; DTC data: P2, PFS 11 mos (n=145); Oral agent
Cabozantinib	FDA-approved for medullary thyroid cancer; DTC data: P1, PR 53% (n=15); Oral agent
Sunitinib	FDA-approved for RCC, PNET, GIST; DTC data: P2, PR 28%, SD 46%; TTP 13 mos (n=28); Oral agent
Pazopanib	FDA-approved for RCC, soft tissue sarcoma; DTC data: P2, PR 49% (n=39); Oral agent
Lenvatinib	FDA-approved for differentiated thyroid cancer; P2, PR 50%, PFS 13 mos (n=58); Oral agent

Dosing and Administration[1]

- Dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before, or 2 hours after a meal). Continue treatment until patient is no longer benefiting from therapy or unacceptable toxicity.
- Temporary interruption is recommended in patients undergoing major surgical procedures.
- Temporary interruption or permanent discontinuation may be required for the following:
    - Cardiac ischemia or infarction
    - Hemorrhage requiring medical intervention
    - Severe or persistent hypertension despite adequate anti-hypertensive therapy
    - Gastrointestinal perforation
    - QTc prolongation
    - Severe drug-induced liver injury

Table 1. Dose modifications in DTC

Dose reduction	Sorafenib dose	
First dose reduction	600 mg daily dose	400 mg and 200 mg 12 hours apart (2 tablets and 1 tablet 12 hours apart – either dose can come first)
Second dose reduction	400 mg daily dose	200 mg twice daily (1 tab twice daily)
Third dose reduction	200 mg daily dose	200 mg once daily (1 tab once daily)

Table 2. Dose modifications for dermatologic toxicities in DTC

Dermatologic toxicity grade	Occurrence	Sorafenib dose modification
Gr 1: numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib
Gr 2: painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Decrease sorafenib dose to 600 mg daily; if no improvement within 7 days, see below
	No improvement within 7 days at reduced dose OR 2nd occurrence	Interrupt sorafenib until resolved or improved to grade 1; if sorafenib is resumed, decrease dose (see Table 1)
	3rd occurrence	Interrupt sorafenib until resolved or improved to grade 1; if sorafenib is resumed, decrease dose (see Table 1)
	4th occurrence	Discontinue sorafenib permanently
Gr 3: moist desquamation, ulceration, blistering, or severe pain of the hands or feet, resulting in inability to work or perform activities of daily living	1st occurrence	Interrupt sorafenib until resolved or improved to grade 1; if sorafenib is resumed, decrease dose by one dose level (see Table 1)
	2nd occurrence	Interrupt sorafenib until resolved or improved to grade 1; when sorafenib is resumed, decrease dose by 2 dose levels (see Table 1)
	3rd occurrence	Discontinue sorafenib permanently

- Following improvement of Gr 2 or 3 dermatologic toxicity to Gr 0-1 after at least 28 days of treatment on a reduced dose of sorafenib, the dose of sorafenib may be increased one dose level from the reduced dose. Approximately 50% of patients requiring a dose reduction for dermatologic toxicity are expected to meet these criteria for resumption of the higher dose and roughly 50% of patients

resuming the previous dose are expected to tolerate the higher dose (that is, maintain the higher dose level without recurrent Gr 2 or higher dermatologic toxicity).

Safety [1]
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Known severe hypersensitivity to sorafenib or other components • Sorafenib in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer
Warnings/Precautions	• Risk of Cardiac Ischemia and/or Infarction. Incidence of cardiac ischemia/infarction was 1.9 vs. 0% in the sorafenib vs. placebo-treated arms of the DTC study. Patients with unstable CAD or recent MI were excluded from the study. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischemia and/or infarction. • Risk of Hemorrhage. In the DTC trial, the incidence of bleeding was 17.4 vs. 9.6% of patients receiving sorafenib vs. placebo, respectively. However, Grade 3 bleeding occurred in 1 vs. 1.4% of these patients. Consider permanent discontinuation of sorafenib if bleeding necessitates medical intervention. Tracheal, bronchial, and esophageal infiltration should be treated with local therapy prior to initiation of sorafenib, due to the potential risk for bleeding. • Risk of Hypertension. In the DTC study, HTN was reported in 40.6 vs. 12.4% of sorafenib vs. placebo-treated patients. HTN was mild to moderate, noted early in the course of treatment and managed with antihypertensive therapy. Monitor blood pressure weekly during the first 6 weeks of sorafenib therapy. Thereafter, monitor blood pressure and treat HTN according to standard medical practice. Consider temporary or permanent discontinuation of sorafenib in cases of severe or persistent HTN despite antihypertensive therapy. Permanent discontinuation was noted in 1 of 207 patients in the DTC trial. • Risk of Dermatologic Toxicities. The most common dermatologic toxicities noted with sorafenib include hand-foot skin reaction and rash. They typically appear during the first 6 weeks of therapy and are Grade 1 or 2 severity. Management may include topical therapies, treatment interruption and/or dose modification. In severe cases, permanent discontinuation may be needed, as was noted in 5.3% (11 of 207) of sorafenib-treated patients in the DTC trial. • Risk of Gastrointestinal (GI) Perforation. GI perforation is an uncommon event; reported in < 1% of patients taking sorafenib. • Warfarin. Infrequent bleeding or INR increases have been reported in patients taking warfarin while on sorafenib. Monitor patients taking concomitant warfarin for changes in prothrombin time, INR or clinical bleeding. • Wound Healing Complications. Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures. The decision to reinitiate sorafenib post-surgery should be based upon clinical judgment of adequate wound healing. • Increased mortality observed with sorafenib administered in

	combination with carboplatin/paclitaxel and gemcitabine/cisplatin in squamous cell lung cancer. • Risk of QT Interval Prolongation. Sorafenib can prolong the QT/QTc interval, which increases the risk for ventricular arrhythmias. Avoid sorafenib in patients with congenital long QT syndrome. Monitor electrolytes and electrocardiograms in patients with CHF, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Correct electrolyte abnormalities (magnesium, potassium, calcium). Interrupt sorafenib if QTc interval is greater than 500 milliseconds or for an increase from baseline of 60 milliseconds or greater. • Drug-Induced Hepatitis. Sorafenib can cause a hepatitis characterized by a hepatocellular pattern of liver damage with significant increases in transaminases which may result in hepatic failure and death. Increases in bilirubin and INR may also occur. In a global monotherapy database, the incidence of severe drug-induced injury was 0.06%. Monitor liver function tests regularly, should significant increases in transaminases occur without alternative explanation, such as viral hepatitis or progressive malignancy, discontinue sorafenib. • Embryo-fetal Risk. Sorafenib may cause fetal harm when administered to a pregnant woman. Advise women of childbearing potential to avoid becoming pregnant while on sorafenib due to the potential hazard to the fetus. • Impairment of Thyroid Stimulating Hormone Suppression in DTC. Sorafenib impairs exogenous thyroid suppression. In the DTC study, 99% of patients had a baseline thyroid stimulating hormone (TSH) level less than 0.5 mU/L. Elevation of TSH level above 0.5 mU/L was noted in 41 vs. 16% of sorafenib vs. placebo-treated patients, respectively. The median maximal TSH in affected patients was 1.6 mU/L with 25% having levels greater than 4.4 mU/L. Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

Safety Considerations

- Adverse events led to the following in DECISION (sorafenib vs. placebo): dose interruption (66 vs. 26%), dose reduction (64 vs. 9%), withdrawal (19 vs. 4%)
- Hand-foot skin reaction was the most common reason for interruptions, reductions and withdrawals
- The mean daily dose of sorafenib was 651 mg (SD 159) and 793 mg (SD 26) of placebo.
- Most adverse events were grades 1 and 2 and occurred early in the course of treatment.
- Patient/caregiver education and diligent monitoring, especially during the first 6 weeks of therapy, will be important when prescribing sorafenib.
- Careful consideration of patient history and comorbidities, particularly with regard to potential toxicities consistent with VEGF inhibition (i.e. risk of bleed, HTN, impaired wound healing).

Adverse Reactions

Common adverse reactions	Incidence $\geq$ 20%: diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pain, hypertension and hemorrhage.
Death/Serious adverse	Grade 3 and 4: Hand-foot skin reaction, HTN, Diarrhea, Fatigue, Weight

reactions	loss
Discontinuations due to adverse reactions	14% (vs. 1.4% in the placebo arm)

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 2015) using the search terms sorafenib and Nexavar. The search was limited to studies performed in humans and published in the 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.

Review of Efficacy in DTC

Sorafenib vs. Placebo

Study design	Inclusion/Demographics	Intervention	Outcomes
DECISION[2] R, DB, MC, PC, P3 N=417 77 centers; 18 countries	Inclusion Age ≥ 18 yrs; LA or metastatic radioactive iodine-refractory DTC, progressive disease, ECOG PS 0-2, adequate bone marrow, liver and renal function, TSH < 0.5 mIU/L Exclusion Prior targeted therapy, thalidomide or chemo for thyroid cancer; low-dose chemo for radiosensitization permitted Demographics Median age 63 yrs (24-87) ≥ 60 yrs (61%) White ~60% Asian ~23% Distant mets ~96%	Sorafenib 400 mg PO BID vs. placebo PO BID Stratified by age (<60 vs. ≥ 60 yrs) and geography (North America vs. Europe vs. Asia) Treatment until PD, toxicity, non-compliance or withdrawal Tumor assessment q8wks with RECIST criteria	Sorafenib 400 mg PO BID vs. placebo PO BID Primary endpoint: PFS Secondary: OS, TTP, ORR, DCR, DOR, safety Median follow-up 16 mos: Central review PFS 10.8 vs. 5.8 mos [HR 0.59 (0.45-0.76); p<0.0001] Investigator-assessed PFS 10.8 vs. 5.4 mos [HR 0.49 (0.39-0.61); p<0.0001] OS not significant [HR 0.80 (0.54-1.19); p=0.14] ORR (all PR) 12.2 vs. 0.5% (p<0.0001) DCR 54.1 vs. 33.8% (p<0.0001) TTP 11 vs. 5.7 mos [HR 0.56 (0.43-0.72); p<0.0001] DOR 10.2 mos (7.4-16.6) Tx duration 10.6 vs. 6.5 mos SAEs (Gr 3, 4): 37 vs. 26% HFS 20 vs. 0 Diarrhea 5.8 vs. 1% Rash 4.8 vs. 0 Fatigue 5.3 vs. 1.4% Weight loss 5.8 vs. 1% HTN 9.7 vs. 2.4% Hypocalcemia 9.2 vs. 1.5%

Paschke, et al.[3]
Evaluate BRAF and RAS mutations in DECISION as prognosticators, determinant of response
N=256
126 sorafenib;
130 placebo
	Same population as above	Archived tumor samples were analyzed for 238 mutations in 19 common oncogenes	mBRAF 30%; mRAS 19%; no mutations 47%
			<u>sorafenib arm</u>
			wtBRAF (n=92): HR = 0.55, p < 0.001;
			mBRAF (n=34): HR = 0.46, p = 0.02;
			(interaction p-value = 0.65)
			
			wtRAS (n=102): HR = 0.60, p = 0.004;
			mRAS (n=24): HR = 0.49, p = 0.045;
			(interaction p-value = 0.42)
			
			Neither BRAF or RAS mutations were independently prognostic for PFS

R Randomized DB Double-Blind, MC Multicenter, PC Placebo-controlled, P3 phase 3, OL open label, P2 phase 2, LA locally advanced, DTC disseminated thyroid carcinoma, TSH thyroid stimulating hormone, TTP time to progression, DCR disease control rate, DOR duration of response

- DECISION was a phase 3 trial comparing sorafenib vs. placebo in patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer. The primary endpoint of PFS was significantly increased in the sorafenib arm (both via central and investigator-review).
- Overall survival, a secondary endpoint, was not reached and did not differ significantly between groups. The majority of patients (71%) in the placebo group crossed over to receive open-label sorafenib at time of progression.
- An exploratory analysis of subgroups shows the overall point estimate favors sorafenib use in the specified groups in this trial; Disease control rate, as well as time to progression was prolonged in the sorafenib arm.
- No Quality of Life data have been presented.

Other Considerations

- Updated ATA Guidelines for the Management of Thyroid Nodules and Differentiated Thyroid Cancer are still in development. A specific release/publication date is not available at this time. The 2009 Guideline note potential benefit with anti-angiogenic therapies that have numerous common side effects. Although noted that these toxicities are responsive to supportive care measures, suggest that treatment with these agents should be limited to specialists experienced in their use.
- NCCN Guidelines list sorafenib as a category 2A recommendation in iodine-refractory, recurrent, locally advanced or soft tissue/bony metastatic disease; NCCN also notes that other small molecule TKI's (axitinib, pazopanib, sunitinib, vandetinib) can be considered if clinical trials are not available or appropriate.
- NCCN also provides Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer, which points out that several factors should be considered regarding TKI therapy:
    - Therapy is not curative, but can prolong PFS
    - Therapy can be expected to cause significant side effects that can affect quality of life
    - The natural history of DTC and MTC is variable, ranging from months to years
    - Pace of disease progression should be considered as those asymptomatic with indolent disease may not benefit; those with rapidly progressive disease may benefit despite side effect profile
    - Optimal management of kinase inhibitor side effects is essential; guidelines to address dermatologic, hypertensive and GI side effects can be used, as well as dose modification and holding therapy

Projected Place in Therapy

- Thyroid cancer is considered rare in the U.S. The lifetime incidence of developing thyroid cancer is less than 1%. It is estimated that 63,000 new cases will be diagnosed in in the U.S. in 2014; resulting in 1900 deaths. It is more commonly seen in women and ranks as the 5th most common malignancy among women. The peak age of incidence is 49 years.
- Three main types of thyroid cancer are: differentiated (includes papillary, follicular, Hurthle), medullary and anaplastic (undifferentiated). Differentiated thyroid cancers are the most common (>90%) followed by medullary (~4%) and anaplastic (~2%).
- Overall, DTC is the least aggressive type of thyroid cancer and has an excellent prognosis, although a small percentage of patients will have more aggressive disease. Five-year survival rates are best among patients with local or regional disease (96-99%), whereas those with distant disease fare worse (56%).
- Factors associated with poorer prognosis in DTC include: age > 45 years, male gender, radioactive iodine resistance, PET scan with positive FDG uptake.
- Genetic alterations within the MAPK and/or PI3 signaling pathways have been identified in the pathogenesis of thyroid cancer. VEGF is a noted contributor to progression. The focus of research has been on the development of novel agents that affect these targets.
- Cytotoxic chemotherapy has a very limited role, if any, in the management of thyroid cancer. International guidelines no longer support its use.
- Multiple tyrosine kinase inhibitors have activity in thyroid cancer, though not all have FDA-approval for this indication.
- Some patients exhibit an indolent course of disease with minimal to no symptoms. There does not appear to be a benefit of targeted therapy in these patients, as there is a great risk of toxicity. No benefit in overall survival or quality of life has been shown to date. In symptomatic patients with an aggressive disease course, the potential benefit of disease stabilization needs to be weighed against the toxicity profile and commitment to intensive management strategies.

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Appendix 1: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.