National PBM Drug Monograph

Sunitinib (Sutent®)

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

Executive Summary:

Efficacy

- Sunitinib is a multikinase inhibitor that targets the VEGF receptor and PDGF receptor tyrosine kinases as well as other tyrosine kinases
- It is metabolized by CYP3A4 to an active metabolite, and may be affected by inhibitors and inducers of the CYP3A4 enzyme family.
- Bioavailability is not affected by food
- The oral regimen is 50mg daily for 4 consecutive weeks followed by 2 weeks off therapy for a treatment cycle equal to 6 weeks.
- In GIST patients intolerant to or resistant to imatinib, sunitinib demonstrated significant improvement in time to progression versus placebo (24 weeks vs. 5.1 weeks) and overall survival (40 weeks vs. 15.9 weeks) in a phase III trial
- In MRCC patients who failed on 1 previous cytokine based therapy, sunitinib produced partial responses in 34% and stable disease in 29% of patients. The duration of response has not yet been reached. Progression free survival, a secondary endpoint, was 8.3 months. The true meaning of response rate in renal cell carcinoma is still being debated.

Safety

- Common adverse events include fatigue, skin discoloration, hand-foot syndrome, hypertension, nausea, vomiting, and abdominal pain. Most events are Grade 1 or 2, with a few Grade 3 (fatigue, leucopenia, elevated lipase) and rare Grade 4.
- Blood pressure should be monitored and hypertension should be treated with standard therapy
- Skin regimens that include the liberal use of emollients on hands and feet may be useful in preventing and treating some of the skin adverse events
- Hematologic abnormalities, sometimes Grade 3, generally resolve during the 2 weeks off therapy
- Rare decreases in LVEF may be transient in some patients or require treatment in others. It is unknown if risk factors for cardiac disease predispose patients to this adverse event.

Cost

- Sunitinib therapy costs are similar to the costs for sorafenib. Comparison to high-dose IL-2 therapy is difficult as that therapy requires inpatient intensive care throughout.

Recommendations

- It should be available for use in GIST patients intolerant to or resistant to imatinib therapy
- It should be available for first-line use in MRCC patients who are not candidates for high-dose IL-2. Consider it for second-line use after progression on first-line sorafenib.
- A baseline evaluation of ejection fraction should be considered for all patients and is recommended for those with any cardiac history. Patients with known cardiac disease or cardiac risk factors should have cardiac function monitored regularly
- Blood pressure should be monitored regularly and treated with standard therapy if elevated

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 sunitinib 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

Sunitinib is an oral multikinase inhibitor that inhibits vascular endothelial growth factor receptors 1-3 (VEGFR) and platelet-derived growth factor receptors α and β (PDGFR) as well as other tyrosine kinases like c-KIT and FLT-3. Receptor tyrosine kinases are implicated in tumor growth and progression.

Table #1 Pharmacokinetic Parameters

Parameter	Drug
Metabolism	Metabolized by CYP3A4 to a primary active metabolite (SU012662) that is further metabolized by CYP3A4; sunitinib does not inhibit or induce any major CYP enzymes
Elimination	Primarily in feces (61%); renal elimination accounts for 16%
Half-life	Terminal t½ = 40-60 hours for sunitinib, 80-110 hours for metabolite SU012662
Protein Binding	Binding of parent and metabolite to human plasma protein = 95% and 90%, respectively
Bioavailability	Is not affected by food

Early pharmacokinetic and safety data found that AUC increased less than proportionally with dose increases. A simulation was run using observed AUC values from the dose escalations adjusted to fixed doses of sunitinib. The amount of variability between the AUC from BSA normalized and fixed doses were comparable at days 1 and 28 for both the parent drug and major metabolite. Dose-limiting toxicities were associated with combined trough levels of sunitinib and SU-12662 ≥100 mcg/mL. Sunitinib doses of 50 mg/day produce plasma concentrations of 50-100 mcg/mL.[1]

FDA Approved Indication(s) and Off-label Uses

1. Treatment of gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylate.

2. Treatment of advanced renal cell carcinoma (MRCC). Approval is based on partial response rates and duration of responses. There are no randomized trials of sunitinib showing increased survival or improvement in disease-related symptoms.

Current VA National Formulary Alternatives

1. High-dose Interleukin-2 (aldesleukin)
2. Interferon alpha

Dosage and Administration

The recommended dose of sunitinib for both GIST and advanced renal cell carcinoma is one 50mg capsule orally once a day, on a schedule of 4 weeks of treatment followed by 2 weeks off treatment. Sunitinib may be taken with or without food.

Pharmacokinetic analysis found that age, body weight, creatinine clearance, race, gender, or ECOG performance score do clinically affect sunitinib pharmacokinetics.

Dose increases or decreases of 12.5mg increments are recommended based on safety and tolerability. Sunitinib is available as a 12.5 mg, 25mg, and 50mg capsule.

Strong CYP3A4 inhibitors (e.g. ketoconazole) may increase sunitinib plasma concentrations. A dose reduction to a minimum of 37.5mg should be considered if sunitinib must be administered with a strong CYP3A4 inhibitor. Alternatively, selection of a medication with no or minor enzyme inhibition should be considered.

Strong CYP3A4 inducers (e.g. rifampin) may decrease sunitinib plasma concentrations. A dose increase to a maximum of 87.5mg should be considered if sunitinib is co-administered with a strong CYP3A4 inducer and the patient carefully monitored for toxicity. Alternatively, selection of a medication with no or minor enzyme induction potential should be considered. The reduction in sunitinib plasma levels when given with St. John's Wort is unpredictable. St. John's Wort should not be administered with sunitinib.

Hepatic Insufficiency: No clinical trials were performed in patients with impaired liver function. Clinical trials excluded patients with ALT or AST values >2.5 times the upper limit of normal (ULN), or if liver function abnormalities were due to the underlying disease, >5.0 times ULN.

Renal Insufficiency: No clinical trials were performed in patients with renal insufficiency. Clinical trials excluded patients with serum creatinine > 2.0 times ULN. Pharmacokinetic studies found that pharmacokinetics were unaltered in patients with calculated creatinine clearances of 42-347 mL/min.

Pediatric Patients: There are no pharmacokinetic studies in pediatric populations.

Efficacy

A. Renal Cell Carcinoma

Efficacy Measures

1. Pivotal Trial (multicenter, open-label, single arm) N=106 (1006) [2]

- Primary Objective: Response Rate (antitumor efficacy) in patients with metastatic RCC refractory to 1 prior cytokine therapy (interferon-alpha, IL-2, or the combination)
- Secondary Objectives: Duration of Response, Progression-Free Survival (PFS), Overall Survival (OS), Safety

2. Supportive Trial (Phase II, multicenter, open-label) N=63 (014) [3]

- Primary Objective: Response Rate in patients with metastatic RCC after failure of 1 cytokine therapy (interferon-alpha or IL-2) or unacceptable toxicity
- Secondary: Assessment of sunitinib plasma levels and biomarkers, duration of treatment, safety, Quality of Life (QoL)

3. Supportive Trial (Phase III, MC, R versus interferon in first-line therapy) N=750[4]

- Primary Objective: Progression Free Survival in patients with metastatic RCC who received no prior systemic therapy
- Secondary: Objective Response Rate, Overall Survival, Patient-reported outcomes, Safety

Summary of efficacy findings

1. RCC Pivotal Trial

- Sunitinib was given as 50mg per day, orally, for 4 consecutive weeks followed by 2 weeks off treatment for a 6 week cycle.
- Dose reduction to 37.5mg then to 25mg was allowed for toxicity
- Therapy was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Table #2 RCC Pivotal Trial

Outcome	Independent Assessment	Investigator Assessment
Response Rate		
Complete Response		1%
Partial Response	34% (95%CI 25-44)	43%
Overall Response (CR+PR)	34%	44% (95%CI 34-53)
Stable Disease	29%	22%
Progressive Disease or SD < 3 months	37%	34%
Duration of Response	Not yet reached	10 months (95%CI 8-not calculable)
Progression Free Survival (PFS)	8.3 months (95%CI 7.8-14.5)	8.1 months (95%CI 5.5-10.4)
6 month survival	79% (95%CI 70-86)	

- Median Overall Survival (OS) has not yet been reached.
- Median number of 6 week cycles completed was 5 (range 0-11)
- The most common reported adverse events were diarrhea and fatigue
- Others included stomatitis, hand foot syndrome, hypertension, neutropenia without fever or sepsis, elevated lipase levels
- 8 patients (4.7%) had a decline in the left ventricular ejection fractions assessed by MUGA scan. Five had a decrease from baseline of 20% or more and to less than the lower limits of normal but without clinical signs or symptoms of congestive heart failure.
- 31 patients died, 10 within 28 days of their last dose of sunitinib, and 1 patient died from a myocardial infarction thought to be due to sunitinib therapy.
- Pooled analysis of the pivotal phase II trial and supportive phase II trial for prognostic features for response and progression free survival found a higher proportion of patients responded if they had normal baseline hemoglobin and/or a baseline ECOG score of 0 vs 1. A univariate analysis showed a longer progression free survival in patients with a favorable ECOG Performance Status, normal hemoglobin level, and other clinical features. A low baseline hemoglobin was in independent predictor of a shorter progression free survival in a multivariate analysis.

2. Supportive Phase II trial

- Sunitinib was administered at 50mg per day orally for 4 consecutive weeks, followed by 2 weeks off therapy for a 6 week cycle.
- Dose escalation increments of 12.5mg per day, up to 75mg per day were allowed in the absence of treatment-related toxicity.
- Dose reductions to 37.5mg and then 25mg were allowed for toxicities

Table #3 RCC Supportive Trial

Outcome	Sunitinib Patients
Response Rate	
Partial Response	40% (95%CI 28-53)
Stable Disease	27%
Progressive Disease or SD < 3months	33%
Median time to first observation of PR	2.3 months

Median Time to Progression	8.7 months (95%CI 5.5-10.7)
Median Survival	16.4 months (95%CI 10.8-not yet reached)

- Median duration of treatment was 9 months
- The most common adverse events were fatigue and diarrhea
- The most common laboratory abnormalities were lymphopenia without infection and elevated lipase without signs and symptoms of pancreatitis.
- 4 patients were removed from the study due to a decline in cardiac ejection fraction; only 1 patient had signs or symptoms of decreased ejection fraction (dyspnea)
- 35% of patients required one dose reduction; 2 patients required a second dose reduction
- 5 patients had a dose escalation to 62.5mg, and 1 to 75mg per day.
- Quality of Life (QoL) Scores: Baseline health state visual analogue scale (VAS) scores were similar to those of an age-matched US general population, and did not change substantially from baseline through the 24 weeks of therapy. Fatigue scores (FACIT-fatigue) were similar at baseline and throughout the 24 weeks, but seemed to increase during treatment and return to baseline levels during the 2 weeks off therapy.
- Trough plasma levels of the parent compound and active metabolite were achieved and maintained throughout multiple dosing cycles within the range shown to inhibit the target kinases in preclinical studies.
- Tumor imaging suggests sunitinib causes qualitative changes in contrast uptake that precede or accompany regression of the tumor.

3. Supportive Phase III trial

- Sunitinib was administered at 50mg per day for 4 consecutive weeks followed by 2 weeks off for a cycle length of 6 weeks.
- Interferon alfa-2a was administered subcutaneously three times a week on nonconsecutive days at 3 million units per dose the first week, 6 million units per dose the second week, 9 million units per dose thereafter

Table #4 Phase III trial versus interferon in RCC

Outcome	Sunitinib (N=375)	Placebo (N=375)
Objective Response Rate % Complete Response Partial Response Stable Disease Progressive Disease	 0 31 48 21	 0 6 49 45
Progression Free Survival Median 95% CI Hazard Ratio 95% CI P	 11 months 10-12 0.42 0.32-0.54 <0.001	 5 months 4-6
Overall Survival Hazard Ratio for death 95%CI P	Not yet reached 0.65 0.45-0.94 0.02	Not yet reached

- The comparison for overall survival did not yet reach the prespecified level of significance in an interim analysis
- When prognostic factors were analyzed the benefit of sunitinib was observed in all subgroups.
- Health related quality of life was significantly better in the sunitinib group as reported by patients in post-baseline assessments (FACT-G and FKSI)
- 38% of sunitinib patients and 32% of interferon patients required a dose interruption for adverse events
- 32% of sunitinib patients and 21% of interferon patients required a dose reduction for adverse events
- At the time of analysis, 66% of sunitinib patients continued on therapy versus 34% of interferon patients
- Withdrawal due to disease progression occurred in 25% of sunitinib patients and 45% of interferon patients ($p<0.001$)
- Withdrawal due to adverse events occurred in 8% of sunitinib patients and 13% of interferon patients ($p=0.05$)

- A grade 3 decline in Left Ventricular Ejection Fraction was seen in 3% of sunitinib patients and 2% of interferon patients. The decline was reversible in the sunitinib group either through dose modification or dose discontinuation and never produced clinical symptoms.

B. Gastrointestinal Stromal Tumors (GIST)

Efficacy Measures[5]

1. Pivotal Trial (randomized, double-blind, phase III, multicenter) N=312 (1004)

- Primary Objective: Compare Time to Progression (TTP) of sunitinib plus best supportive care (BSC) to BSC alone for treatment of patients with imatinib resistant or intolerant GISTs.
- Secondary Objectives: Overall survival, progression free survival, response rate, time to tumor response, duration of response, duration of performance status maintenance, safety and tolerability, exposure blood levels of parent drug and active metabolite, correlate biomarkers with outcomes, compare pain control, analgesic use, tumor related signs and symptoms, health status, and performance status in both arms

2. Supportive Trial (Phase I/II, sponsor conducted, open-label, multicenter, single arm) N=55 (013)

- Primary Outcome: Safety and Efficacy in GISTs following failure on imatinib therapy
- Secondary Outcome: Evaluate fatigue/asthenia using FACIT-Fatigue scale

Summary of efficacy findings

1. GIST Pivotal Trial

- Patients received Sunitinib 50mg orally or placebo daily for 4 consecutive weeks, followed by 2 weeks off therapy for each 6 week cycle.
- Unblinding and crossover was available for patients meeting the RECIST criteria for disease progression, had an ECOG performance status of 0-2, and no severe, acute, or chronic conditions that would increase risk associated with participation in the study.

Table #5 GIST Pivotal Trial

Outcome	Sunitinib N=202	Placebo N=102
TTP (median) Hazard Ratio 95%CI P-value	24 weeks 0.363 (0.26-0.51) 0.0001	5.1 weeks
PFS (median) Hazard Ratio 95%CI P-value	24.1 weeks 0.334 0.24-0.465 <0.0001	6.0 weeks
ORR (median) 95%CI	6.8 3.7-11.1	0
OS (median) Hazard Ratio 95%CI p-value	40 weeks 0.491 0.290-0.831 0.007	15.86 weeks

- Subgroup analysis of TTP found similar results to the entire population with subgroups based on age, gender, race, and trial site.

2. Supportive Trial

- Patients received Sunitinib 50mg per day orally for 4 consecutive weeks followed by 2 weeks off therapy for a 6 week cycle.
- Partial Response Rate= 9.1% (95%CI 3.0-20.0)
- Median TTP= 34 weeks (95%CI 22-38.6)
- Median OS= 85.1 weeks (58.9-108.1)

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 17).

Adverse Events (Safety Data)

Table #6 Adverse Events reported in at least 10% of GIST patients

Adverse Event (%)	Sunitinib =202		Placebo N=102	
	All Grades	Grade 3 or 4	All Grades	Grades 3 or 4
Constitutional				
Fatigue	42	8	47	8
Fever	18	2	17	1
GI				
Diarrhea	40	4	27	0
Nausea	31	2	32	5
Mucositis	29	1	18	2
Vomiting	24	2	24	3
Constipation	20	0	14	2
Abd pain	33	11	38	12
Hypertension	15	4	11	0
Derm				
Rash	14	1	9	0
Skin Discoloration	30	0	23	0
Hand-foot syndrome	14	4	10	3
Neurology				
Altered Taste	21	0	12	0
Headache	13	2	23	0
Musculoskeletal				
Arthralgia	12	1	16	0
Back pain	11	1	16	4
Myalgia	14	1	9	1
Respiratory				
Dyspnea	10	0	19	3
Cough	8	0	13	0
Metabolism				
Anorexia	33	1	29	5
Asthenia	22	5	11	3
Hemorrhage/bleeding				
Bleeding, all sites	18	7	17	9

Table #7 ≥10% Treatment related laboratory abnormalities

Adverse Event (%)	Sunitinib		Placebo	
	All Grades	Grades 3 or 4	All Grades	Grade 3 or 4
GI				
AST/ALT	39	2	23	1
Alk Phos	24	4	21	4
T. Bili	16	1	8	0
I. Bili	10	0	4	0
Amylase	17	5	12	3
Lipase	25	10	17	7
Cardiac				
Decreased LVF	10	1	3	0
Renal				
Creatinine	12	1	7	0
Hypokalemia	12	1	4	0
Hyponatremia	10	0	4	1
Uric Acid	15	8	16	8
Hematology				
Neutropenia	53	10	4	0
Lymphopenia	38	0	16	0
Anemia	26	3	22	2
Thrombocytopenia	38	5	4	0

Table #8 Treatment Related Adverse Events in MRCC in at least 10% of patients

Adverse Event (%)	Sunitinib N=169	
	All Grades	Grades 3 or 4
Constitutional		
Fatigue	74	11
Fever	15	1
GI		
Diarrhea	55	5
Nausea	54	2
Mucositis	53	4
Dyspepsia	46	1
Vomiting	37	4
Constipation	34	1
Abdominal pain	20	3
Glossodynia	15	0
Flatulence	14	0
Cardiac		
Hypertension	28	6
Peripheral Edema	17	1
Derm		
Rash	38	1
Skin discoloration	33	0
Dry Skin	17	0
Hair color change	17	0
Hand-foot syndrome	12	3
Alopecia	12	0
Neurology		
Altered taste	43	0
Headache	25	1
Dizziness	16	2
Musculoskeletal		
Arthralgia	28	1
Pain in limb	18	1
Back pain	17	1
Myalgia	17	1
Respiratory		
Dyspnea	28	5
Cough	17	1
Metabolism		
Anorexia	31	1
Dehydration	11	3
Hemorrhage		
Bleeding, all sites	26	1

Table #9 Treatment Related Grade 3 and 4 Hematologic Laboratory Abnormalities

Lab Test (%)	Sunitinib in MRCC		
	Grade 3	Grade 4	Grade 3+4
Hematology	32	2	34
Neutropenia	12	1	13
Anemia	5	2	7
Lymphopenia	20	1	21
Thrombocytopenia	3	0	3
Leukopenia	7	0	7

Deaths and Other Serious Adverse Events (optional)

RCC Trials

In the pivotal trial there were 8 deaths within 28 days of discontinuing therapy. One patient developed shortness of breath and cold hands, with ECG changes and enzymes consistent with a myocardial infarction thought to be attributed to the study drug.

In the supportive trial, one death was attributed to progressive disease.

Other Serious Adverse Events (RCC):

Vomiting, abdominal pain, pneumonia, dehydration, failure to thrive, peripheral neuropathy, periorbital edema, appetite disturbance, dyspnea, pleural effusion, renal failure, pain, sepsis, abnormal ejection fraction, speech disorder, prolonged prothrombin time (1), prolonged PTT (1), pulmonary embolism and thrombosis (1)

GIST Trials

Twenty-three patients (11%) in the sunitinib arm (11% on placebo) died during the blinded phase or after discontinuing the blinded phase. Thirteen sunitinib patients died within 28 days of receiving their last dose of study medication.

Other Serious Adverse Events (GIST):
Fifty-seven percent of patients on the sunitinib arm and 52% of patients on placebo experienced grade 3 or 4 adverse events. Grade 4 events occurred in 15% of patients in each arm.

Common Adverse Events

Hypertension, gastrointestinal disturbances, skin abnormalities, altered sense of taste, asthenia, decreased ejection fraction, arthralgia, and mucositis

Other Adverse Events

1. Reduction in Left Ventricular Ejection Fraction: In the GIST trial, 11% of sunitinib patients (versus 3% of placebo patients) experienced treatment related LVEF values below 50% (grade 2 or higher on the NCI-CTCAE). Of those patients, 41% had recovery of LVEF to normal range without intervention, 23% had recovery of LVEF to normal range with intervention, 27% had no documented recovery of LVEF to normal range, and 9% died.
   In the MRCC trials, 15% of patients had decreases in LVEF values to below the lower limit of normal at some time during therapy. Most changes were mild or transient. Seven patients had more severe changes and reversibility was not determined or inadequately documented.
2. Adrenal Insufficiency: No clinical evidence of adrenal hemorrhage or necrosis that was seen in early animal studies. There may be a rare incidence of adrenal toxicity demonstrated by abnormal ACTH stimulation test results in GIST patients.
3. Data from non-clinical trials indicates sunitinib may prolong the QT interval. In the GIST study, QT prolongation (> 20 milliseconds from baseline) occurred in 11% of sunitinib patients and 12% of placebo patients. No clinically significant QT prolongation has been observed in clinical trials.
4. Venous Thromboembolic Events: Four patients in the MRCC trials developed venous thromboembolic events: 2 with deep vein thrombosis and 2 with pulmonary embolism. Seven patients in the GIST trial on sunitinib developed venous thromboembolisms: 5 developed Grade 3 DVT's and 2 were Grade 1 or 2.
5. Seizures: Seizures have been observed in patients on sunitinib with radiographic evidence of brain metastases. There are rare (<1%) reports of patients on sunitinib with seizures and radiographic evidence of reversible posterior leukoencephalopathy syndrome (RPLS) but no fatal outcome. Patients with seizures and signs/symptoms of RPLS (hypertension, headache, decreased alertness, altered mental functioning, and visual loss) should be managed medically including hypertension, and sunitinib should be temporarily suspended. Reinstitution of sunitinib should be at the discretion of the physician.
6. Hypothyroidism: Seven percent of patients in the MRCC trials and 4% in the GIST trials had either clinical or laboratory evidence of hypothyroidism.

7. Hematologic events: Grade 3 neutropenia was observed in 13% of MRCC patients and 9% of GIST patients. Grade 4 neutropenia was observed in 1% of MRCC patients and 2% of GIST patients. Grade 3 and 4 thrombocytopenia was reported in 3% and 0% of MRCC patients, and 4% and 1% of GIST patients on sunitinib, respectively.
8. Pancreatic Function: Grade 3 and 4 increased in serum lipase were reported in 14% and 2% of MRCC patients, respectively. Grand 3 and 4 increased serum amylase levels were reported in 5% and 1% of MRCC patients, respectively. Increased lipase levels were generally transient. Pancreatitis was observed in <1% of patient in either study population.

Tolerability

GIST: Discontinuation due to adverse events was evenly balanced between treatment arms except for withdrawal due to anemia, liver failure, and metabolic disorders in the sunitinib group.

MRCC: Withdrawal due to: fatigue, MDS, nausea dehydration, tumor resection, epistaxis, wound complication, increased lipase, dyspnea, vomiting, infection, abnormal LVEF (3), confusion, renal failure, spinal cord compression, proteinuria, pathologic hip fracture, motor neuropathy.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 17).

Precautions/Contraindications

Precautions

1. Warnings: Pregnancy Category D - angiogenesis is critical to fetal development; inhibition should be expected to have adverse effects on pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant while receiving sunitinib.

2. Left Ventricular Dysfunction: 15% of patients in the MRCC trials had decreases in LVEF to below lower limits of normal. In the GIST comparative trial, 11% of sunitinib patients and 3% of placebo patients had treatment-related decreases in LVEF to below lower limits of normal. Nine of 22 GIST patients had LVEF recovery without intervention. Five of 22 patients had LVEF recovery with intervention. Six patients went off study without documentation of LVEF recovery. Three patients had LVEF fall to <40% and two died.

Patients with cardiac history in the past 12 months (myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or TIA, or pulmonary embolism) were excluded from clinical trials. It is not known if these patients are at an increased risk for drug-related LVEF dysfunction. These patients should be carefully monitored for signs and symptoms of CHF while receiving sunitinib. Baseline and periodic evaluations of LVEF should be considered during sunitinib therapy. For patients without cardiac risk factors, a baseline ejection fraction should be considered.

In the presence of clinical CHF, discontinue sunitinib therapy. Patients with EF's <50% and >20% below baseline without clinical evidence of CHF should have their sunitinib dose interrupted and/or reduced.

3. Hemorrhagic Events: Bleeding occurred in 26% of patients in the MRCC trial and 18% of patients in the GIST trial, compared to 17% of placebo patients. Epistaxis was the most common hemorrhagic event. Less common was rectal, gingival, upper GI, genital, or wound bleeding. Most events in the MRCC trials were Grade 1 or 2 with one Grade 3 bleed. In the GIST trials, 7% of patients had a Grade 3 or 4 bleed. One patient had a fatal GI bleed during cycle 2. Tumor-related hemorrhagic events have been reported, may occur suddenly, and in the case of pulmonary tumors may be life-threatening. Fatal pulmonary hemorrhage occurred in 2 patients

receiving sunitinib in a non-small cell lung cancer trial with squamous cell histology. Treatment-related tumor hemorrhage was reported in 5 patients in the GIST trial. One patient discontinued therapy; 4 others did not stop therapy or have a dose delay due to intratumoral hemorrhage. Tumor hemorrhage has not been reported in MRCC.

4. Hypertension: All grades were reported in 28% of patients in the MRCC trial and 15% of patients in the GIST trial receiving sunitinib. No grade 4 hypertension was reported. No patients discontinued therapy because of hypertension. Severe hypertension (>200mmHg systolic or 110mmHg diastolic) occurred in 6% of MRCC and 4% of GIST patients, respectively. Patients should have their blood pressure monitored regularly and treated with standard antihypertensive therapy as needed.

5. Adrenal Function: Adrenal toxicity was seen in animal studies, consisting of hemorrhage, necrosis, congestion, hypertrophy, and inflammation. In human clinical trials, over 400 patients received ACTH stimulation tests. In patients with normal baseline tests, one patient developed an abnormal ACTH test result during therapy. Eleven patients with normal baselines developed abnormal test results on the last dose. Physicians should monitor adrenal function in patients experiencing stress like surgery, trauma, or severe infection.

Contraindications

Sunitinib is contraindicated in those patients with hypersensitivity to sunitinib malate or any component of Sutent.

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 sunitinib: gefitinib, sumatriptan, Sinemet, erlotinib, sorafenib, imatinib

LA/SA for trade name Sutent: Sufenta, Sinemet, Subutex, Nipent, Serevent, sufentanil, Alupent

Drug Interactions

Drug-Drug Interactions

1. Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib levels. Grapefruit juice may also increase sunitinib levels. Dose modifications may be needed if administered concomitantly.
2. Inducers of CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease concentrations inconsistently. Dose modifications may be needed if administered concomitantly.

Acquisition Costs

Table #10 Comparison of Acquisition Costs

Drug	Dose	Cost/Day ($) Cost/6 weeks ($)	Cost/6 months ($)
Sunitinib	50mg/d for 4 weeks 2 weeks off therapy (cycle=6 weeks)	160.00/day 4480.00/cycle	17,920.00
Sorafenib	400mg BID daily	107.16 4500.72/6 weeks	18,002.88
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 pharmacoeconomics analyses.

Conclusions

Efficacy

1. Gastrointestinal stromal tumors (GIST): In a phase 3 trial comparing second line therapy with sunitinib versus placebo in an open label trial in patients resistant to or intolerant of imatinib, sunitinib significantly improved the Time to Progression (Primary Objective) versus placebo (24 weeks vs. 5.1 weeks, HR=0.363, P=0.0001). There was also improvement in secondary outcomes of progression free survival, objective response rate, and overall survival. A supportive phase I/II trial found similar partial response rates and durability of response.

2. Metastatic Renal Cell Carcinoma (MRCC): In the pivotal phase 2 trial in patients with MRCC who failed on 1 prior cytokine therapy, sunitinib produced partial responses in 34% of patients, and stable disease in another 29% (Primary Objective). Secondary objectives included Progression Free Survival (8.3 months, median) and duration of response (not yet reached according to independent assessment). Overall survival data are not mature, but at 6 months 79% of patients are still alive.

A supportive phase 2 trial in a similar population reported a 40% partial response rate, stable disease in 27%, progression free survival of 8.7 months, and a time to the first observation of a partial response at 2.3 months.

A supportive Phase III trial comparing sunitinib to interferon in patients with metastatic RCC who had not received systemic therapy produced partial responses in 31% and stable disease in 48% versus 6% and 49%, respectively in the interferon group. Progression Free Survival, the primary outcome, was 11 months in the sunitinib group versus 5 months in the interferon group with a hazard ratio of 0.42 ($p<0.001$). Median overall survival has not yet been reached, with a trend toward improved survival in the sunitinib group in an interim analysis that did not meet the prespecified level of significance.

Safety:

The majority of adverse events are Grade 1 or 2 with some Grade 3 events, primarily fatigue, hematologic abnormalities, and elevated lipase levels, and rare Grade 4 events. The most common adverse events, fatigue, GI disturbances, skin changes, and hypertension are common in

other drugs that affect the vascular endothelial growth factor or its receptor. These adverse events reflect a new paradigm in oncology (i.e., monitoring and treating blood pressure, and developing new skincare regiments) and will require learning new ways to treat unexpected adverse events.

Of concern are the rare cardiovascular events reported in both the GIST and MRCC trials, especially the decrease in LVEF. Because patients with any significant cardiac history in the previous 12 months were excluded from all of the trials and the decrease in LVEF was sometimes transient, sometimes reversible with and without treatment, and severe in a small number, it will be prudent to closely monitor general populations with more co-morbidities that may have a higher risk for developing a decrease in ejection fraction. In addition, the development of hypertension may contribute to this rare adverse event.

Of interest is a phenomenon of intratumoral cavitation, fistula formation, lethal peritoneal hemorrhage in 1 patient, and infection of a necrotic area in the lung of one patient seen in an early phase I dose escalation trial. There is also evidence that there were changes in tumor perfusion on CAT scans following sunitinib therapy.[1]

Recommendations and Place in Therapy

1. GIST: For patients with GIST that are intolerant of or resistant to imatinib therapy and are not amenable to curative surgical procedures, sunitinib is the only choice currently available for therapy. It produces prolonged progression free survival versus placebo in second line therapy with modest common adverse events. Assessment of baseline cardiac function and ongoing monitoring of cardiac function will be important in the general population.

2. Metastatic Renal Cell Carcinoma: Sunitinib is the second multikinase inhibitor approved for use in advanced (metastatic) renal cell carcinoma. It was approved for use based on response rate and duration of response, not on an effect on survival or patient symptoms. Since approval, data from the study did show a progression free survival of 8.3 months, although this is from a small phase II trial. Response rates in renal cell carcinoma may not equate to a survival advantage as previous cytokine studies had low response rates with some durable increases in survival. Quality of life data from an earlier phase II trial did show no adverse effect of sunitinib treatment on overall quality of life, although fatigue scores tended to increase during therapy and fall during the two weeks off therapy. A recent phase III trial comparing sunitinib to interferon as first-line therapy found that sunitinib produced better responses and a longer progression free survival versus interferon. Median overall survival has not yet been reached, with a trend toward increased survival with sunitinib in an interim analysis.

Changes in LVEF are a concern, because patients with significant cardiac histories were excluded from the trial. There is also a concern about compliance with a regimen that requires 2 weeks off therapy every 6 weeks.

It is difficult to distinguish which patient populations will benefit most from sunitinib versus sorafenib as second-line therapy following progression on cytokine therapy. In first-line therapy, data from a phase III trial found sunitinib to be superior to interferon. Data on the use of sorafenib for first-line therapy is not yet available.

At this time, differentiation of sunitinib and sorafenib in MRCC has not been determined except in first-line therapy. Until we can determine the best populations for each drug, sunitinib inclusion criteria in MRCC include:

1. First-line therapy in patients with metastatic renal cell carcinoma (all prognostic groups at this time) who are not candidates for high-dose IL-2
2. Consider sunitinib as second line therapy in patients who have progressed on first line sorafenib therapy.
3. For all patients, careful consideration should be given to obtaining a baseline evaluation of ejection fraction and it is not recommended for patients with any cardiac history. Close monitoring of cardiac function is recommended for patients with any risk factors for cardiac disease.
4. Patient with adequate hepatic, renal, and hematologic values at baseline.

Patients with brain metastases should be excluded.

Discontinuation: Patients with progressive disease or unacceptable toxicity

Formulary Recommendation: Sunitinib should remain non-formulary at this time, available for use in patients with GIST intolerant to or resistant to imatinib and for patients with metastatic renal cell carcinoma according to criteria above.

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[5] Center for Drug Evaluation and Research Approval Package For: Application Number NDA 21-938 (GIST) NDA 21-968 (MRCC)

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Appendix: Clinical Trials

Clinical Trial Results for Sunitinib in Metastatic Renal Cell Carcinoma (MRCC)

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Motzer 2006 MC, open label, single arm Funding: Pfizer	Inclusion criteria 1. Prior nephrectomy 2. Clear cell histology 3. Measurable disease 4. Failure of 1 cytokine therapy 5. ECOG PS 0 or 1 6. Adequate organ function (heme, hepatic, renal, cardiac) Exclusion criteria 1. Brain metastases 2. Significant cardiac events w/t 12 months prior to study	Sunitinib 50mg/d orally for 4 consecutive weeks followed by 2 weeks off therapy for a 6 week cycle	Age: Median 56 (32-79) Sex: Male 63% ECOG 0 = 55% 1 = 45% # of MSKCC risk Factors 1 = 58% 2 = 42%	N_R = 106 Outcome / Sunitinib Response Rate CR: 0 PR: 34% SD ≥3 months: 29% PD, SD<3mos: 37% Duration of response: Median duration not yet reached PFS 95%CI: 8.3 months 7.8-14.5 6 month Survival 95%CI: 79% 70-86 OS: Not yet reached Pooled Data from pivotal trial plus supportive trial: CR + PR = 42% SD = 24% PD = 34% PFS = 8.2 months Pretreatment clinical features associated with response: normal baseline hemoglobin, ECOG PS=0 Pretreatment clinical features associated with a longer progression free survival in univariate analysis: ECOG PS, normal baseline hemoglobin level, other features Independent predictor of a shorter progression free survival in multivariate analysis: low hemoglobin (HR=0.37)	Median number of cycles =5 (7 mos) Most common treatment related AE's: Diarrhea, fatigue Other: stomatitis, hand-foot syndrome, hypertension, neutropenia (no sepsis or fever), decline in left ventricular ejection fraction on MUGA. 5 patients had a decrease from baseline of 20% or more, but there were no reports of signs and symptoms of heart failure. 31 patients died, 10 within 28 days of their last dose of sunitinib, and 1 died on study of a myocardial infarction
Motzer 2006 MC, open label, Phase II	Inclusion criteria 1. RCC histology 2. Measurable disease 3. Failure of 1	Sunitinib 50mg/d orally for 4 consecutive weeks followed by 2 weeks off therapy	Age: Median 60 (24-87) Sex: Male=68% ECOG 0=54% 1= 46%	N_R = 63 Outcome / Sunitinib Response Rate PR: 40%	Most common: Fatigue (Grade 3 in 11%) Most frequent Grade 3-4 laboratory

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Funding: Pfizer	cytokine-based therapy 4. ECOG PS 0 or 1 5. Normal serum amylase and lipase 6. Normal ACTH stimulation test 7. Adequate renal, hepatic, hematologic, and cardiac function Exclusion criteria 1. Brain metastases 2. Ongoing dysrhythmia, prolongation of QT_c interval, or any significant cardiac event within the previous 12 months	(cycle=6 weeks) Dose escalation to a maximum of 75mg/day or dose reduction to a minimum of 25mg/day was allowed	MSKCC risk factors 0=54% 1=46%	SD ≥3 months 27% PD or SD< 3mos 33% Median time to first observation of partial response 2.3 months TTP 8.7 mos 95%CI 5.5-10.7 Med OS 16.4 months 95%CI 10.8-NA Median duration of treatment=9 months Quality of Life Mean and median VAS scores were similar at baseline and after 24 weeks of therapy Median and mean fatigue scores on the FACIT-Fatigue scale were similar at baseline and through 24 weeks of therapy, but fatigue scores tended to increase during therapy and decrease during the 2 weeks off therapy Patients maintained steady state trough plasma concentrations of the parent drug and its primary metabolite during multiple cycles within the target range shown to inhibit the target receptor in preclinical trials.	abnormalities: Lymphopenia without infection, elevated serum lipase without clinical signs of pancreatitis, 4 patients were removed for a decline in left ventricular ejection fraction Dose reductions in 35% to 37.5mg Two of these had additional reduction to 25mg Dose escalation to 62.5mg in 5 patients and in 1 patient to 75mg with no evidence of improved response
Motzer 2007 R, MC Phase III First-line therapy Supported by Pfizer	Inclusion criteria 1. metastatic renal cell carcinoma-clear cell 2. No previous systemic therapy 3. Measurable disease 4. ECOG 0-1 5. Adequate hematologic, coagulation, hepatic, renal, cardiac function Exclusion criteria 1. Brain metastases 2. Uncontrolled hypertension	Sunitinib 50mg/d orally for 4 consecutive weeks followed by 2 weeks off therapy (cycle=6 weeks) Dose reduction to a minimum of 25mg/day was allowed Versus Interferon alfa-2a SC three times a week on nonconsecutive days at 3 million units per dose the	Sun / PBO Age 62 / 61 M% 71 / 72 ECOG% O 62 / 61 1 38 / 39 MSKCC 0 38 / 34 1-2 56 / 59 ≥3 6 / 7	N_R=750 Outcome: Sunitinib N=375 / Placebo N=375 Response CR % 0 / 0 PR 31 / 6 SD 48 / 49 PD 21 / 45 PFS 11 mos / 5 mos 95%CI 10-12 / 4-6 HR 0.42 95%CI 0.32-0.54 P <0.001 Death 13% / 17%	Grade 3 or 4 fatigue occurred more often in the interferon group Higher rates of Grade 3 diarrhea, vomiting, hypertension, and hand-foot syndrome in sunitinib group Higher rates of pyrexia, chills, myalgia, and influenza-like symptoms in the interferon group Higher rates of leucopenia, neutropenia, and thrombocytopenia in the sunitinib group Dose interruption due to AEs

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
	3. Clinically significant cardiac event or disease in previous 12 months	first week, 6 million units per dose the second week, and 9 million units per dose thereafter Dose reduction to a minimum of 3 million units per dose was allowed		OS Median not yet reached HR 0.65 95%CI 0.45-0.94 P 0.02 HR for OS did not yet reach prespecified level of significance The benefit of sunitinib over interferon was observed across all subgroup prognostic factors. QoL was significantly better in the sunitinib group as reported in post-baseline assessments using both FACT-G and FKSI (P<0.001)	Sunitinib 38% Inteferon 32% Dose reduction due to AEs Sunitinib 32% Interferon 21% Grade 3 decline in LVEF Sunitinib 2% Interferon 1% In sunitinib group, this decline did not result in clinical sequelae and was reversible with dose modification or discontinuation

N_R, Number randomized; MC=multicenter; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MSKCC=Memorial Sloan Kettering Cancer Center; .CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; PFS=progression free survival; OS=overall survival; HR=hazard ratio; MUGA=multigated acquisition scan; ACTH=adrenocorticotropic hormone; TTP=time to progression; VAS=visual analogue scale; FACIT-fatigue=functional assessment of chronic illness therapy-fatigue; SC=subcutaneous; PBO=placebo; FACT-G=Functional Assessment of Cancer Therapy-General; FKSI=FACT-Kidney Symptom Index

Clinical Trial Results for Sunitinib in GIST

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Study A6181004 R, DB, PC, international Phase 3 trial	Inclusion criteria 1. Histopathologically proven GIST, not amenable to therapy with curative intent 2. measurable disease 3. Failure of prior imatinib therapy (progression or intolerant) 4. ECOG PS 0 or 1 5. Adequate organ function (hepatic, hematologic, renal, cardiac) Exclusion criteria 1. Treatment with chemo, chemoembolization, immunotherapy, or investigational drug after imatinib 2. Treatment of resistant disease with surgery, radiotherapy, or cryotherapy 3. Severe/unstable angina, symptomatic CHF, or CVA within 12 months of therapy 4. Ongoing arrhythmia	Sunitinib 50mg/d orally for 4 consecutive weeks followed by 2 weeks off therapy (cycle=6 weeks) plus BSC Vs BSC	Age: Median 58 sunitinib Median 55 placebo Sex: Male 64% sunitinib Male 61% placebo PS: 0 44% sunitinib 46% placebo 1 55% sunitinib 52% placebo 2 1% sunitinib 2% placebo Imatinib outcome S Pl Intolerant 4% 4% PD w/I 6mos 17% 16% PD after 6mos 78% 80%	N_R = 207 sunitinib 105 placebo Outcome | Sunitinib | Placebo TTP | 24.14 wks | 5.14 weeks HR | 0.363 95%CI | 0.258-0.511 P-value | 0.0001 PFS | 24.1 wks | 6.0 weeks HR | 0.334 95%CI | 0.240,0.465 P-value | <0.0001 ORR | 6.8% | 0% P-value | 0.006 OS | 40 weeks | 15.86wks HR | 0.491 95%CI | 0.29, 0.831 P-value | 0.007	Serious AE's in >1 patient: Decrease in LVEF, adrenal suppression, abdominal pain, bleeding Common AE's: gastrointestinal, general disorders (fatigue), metabolism, respiratory, dermatology Decreased LVEF: 22 patients had decreased LVEF values below 50%; 41% of those had LVEF recovery to normal range without intervention; 23% had recovery to normal range with intervention; 27% had no documentation of LVEF recovery prior to going off therapy 3 patients had LVEF Grade 3 reductions to <40%; 1 recovered without intervention, 2 died without receiving any more study drug
RTKC-0511-013 Phase I/II, open label, MC, dose-escalation	1. Histopathologically confirmed GIST intolerant of or progressive disease in imatinib 2. ECOG 0 or 1 3. Adequate organ function (renal,	Phase II dose: Sunitinib 50mg/d orally for 4 consecutive weeks followed by 2 weeks off therapy (cycle=6weeks)	Age: median 55 (30-76) Sex: Male 61.8% ECOG 0=49.1% 1=49.1% 2=1.8%	N_R = 55 Outcome | Sunitinib Response Rate PR | 9.1% SD ≥6 months | 29% TTP | 34 weeks	Most common AE's Fatigue, diarrhea, abdominal pain, nausea, constipation, skin discoloration, hand-foot syndrome, headache, vomiting, abdominal distension, dyspnea, hypertension, stomatitis, dyspepsia, and edema, dermatitis, flatulence, insomnia, lipase increased

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
	hepatic, hematologic, cardiac)				Prospective cardiac monitoring and serial ACTH tests did not identify any major cardiac or adrenal adverse events.

R=randomized; DB=double-blind; PC=placebo controlled; GIST=gastrointestinal stromal tumor; CHF=congestive heart failure; CVA=cerebrovascular accident; BSC=best supportive care; PD=progressive disease; TTP=time to progression; PFS=progression free survival; ORR=objective response rate; OS=overall survival; HR=hazard ratio; AE=adverse event; LVEF=left ventricular ejection fraction;