



## Therapeutic Class Review<sup>SM</sup>

### sorafenib (Nexavar<sup>®</sup>) and sunitinib malate (Sutent<sup>®</sup>)

**July 2006**

**New Products for Review:**

sorafenib (Nexavar<sup>®</sup>) [Bayer/Onyx]

**Dossier Provided by Manufacturer:** Yes

**Dossier Evaluation:** 3

sunitinib malate (Sutent<sup>®</sup>) [Pfizer]

**Dossier Provided by Manufacturer:** Yes

**Dossier Evaluation:** 3

1- dossier w/missing components

2- all components present, except pharmacoeconomic model

3- all components present (comprehensive)

**Available Therapeutic Alternatives: Renal cell carcinoma (RCC)**

Preferred/Formulary	Non-preferred/non-formulary
<b>COVERED UNDER PHARMACY BENEFIT</b>	
interferon alfa-2b (Intron <sup>®</sup> A) [Schering]	interferon alfa-2a (Roferon-A <sup>®</sup> ) [Roche]
	sorafenib (Nexavar <sup>®</sup> ) [Bayer/Onyx]
	sunitinib malate (Sutent <sup>®</sup> ) [Pfizer]
<b>COVERED UNDER MEDICAL BENEFIT</b>	
aldesleukin (Proleukin <sup>®</sup> ) [Chiron]	
bevacizumab (Avastin <sup>®</sup> ) [Genentech]	
gemcitabine (Gemzar <sup>®</sup> ) [Eli Lilly & Co]	

**Available Therapeutic Alternatives: Gastrointestinal stromal tumor (GIST)**

Preferred/Formulary	Non-preferred/non-formulary
<b>COVERED UNDER PHARMACY BENEFIT</b>	
imatinib mesylate (Gleevec <sup>®</sup> ) [Novartis]	sunitinib malate (Sutent <sup>®</sup> ) [Pfizer]

**Reason for Review:**

Determine the formulary status for sorafenib (Nexavar) and sunitinib (Sutent), two new oral multi-kinase inhibitors indicated for the treatment of patients with:

- Advanced renal cell carcinoma (RCC) [sorafenib (Nexavar) and sunitinib (Sutent)]
- Gastrointestinal stromal tumor (GIST) [sunitinib (Sutent)]

## Executive Summary

- Sorafenib (Nexavar) and sunitinib (Sutent) are both approved for the treatment of advanced RCC.
- Sutent is also approved for patients with GIST who fail, or are intolerant of, therapy with imatinib mesylate (Gleevec).
- Both Sorafenib (Nexavar) and sunitinib (Sutent) received accelerated FDA approval.
  - Patients with advanced RCC and GIST have limited treatment options and poor survival.
  - In lieu of trials that measure overall survival, the FDA considered non-randomized clinical studies and viewed improvements in surrogate endpoints (e.g. tumor response) to correlate with a clinical benefit in these patient populations.
- There is a high risk of off-label use for both agents based on the number of ongoing trials in other types of solid tumors.

## Evidence

The following summarizes the evidence for sorafenib (Nexavar) and sunitinib (Sutent).

	<b>Sorafenib (Nexavar)</b>	<b>Sunitinib (Sutent)</b>	
<b>Condition</b>	Advanced RCC	Advanced RCC	GIST
<b>Evidence</b>	Unreliable	Unreliable	Uncertain clinical usefulness
<b>Study Design</b>	Randomized Placebo-Controlled	Open-label	Randomized Placebo-Controlled
<b>Scientific Data Analysis</b>	Significant study design flaws that make evidence unreliable.		
	Lack of clinically relevant endpoints to measure a benefit. Used surrogate markers that do not correlate to overall survival.		
<b>Survival data</b>	No - Survival data is pending. However, results will be unreliable do to significant protocol changes that occurred during the trial.	No	No -- Survival at 6 months was reported, but is unreliable since placebo patients were given the opportunity to “roll-over” to Sutent after reaching endpoint.
<b>Comparative Head-to-head</b>	No	Yes Open-label, head-to-head trial with interferon.	No -- There are no comparative studies with other treatments in patients resistant to treatment with imatinib mesylate (Gleevec) or treatment-naïve patients.
<b>Adverse Events</b> <small>Note: Trials were not designed or powered to detect harms. Therefore, harms data are not reliable of evaluating long-term safety.</small>	- hypertension, - skin reactions - hemorrhage	- fatigue, - diarrhea - nausea - mucositis/stomatitis - dyspepsia - altered taste	- fatigue - diarrhea, - nausea, - anorexia - skin discoloration - vomiting - asthenia - constipation - dysgeusia

*Considerations in Subpopulations:*

- *Pediatrics:* There is no useful evidence to establish the safety and efficacy of sorafenib (Nexavar) and sunitinib (Sutent) in pediatric patients.
- *Geriatrics:* Current clinical experience with sorafenib (Nexavar) and sunitinib (Sutent) has not identified differences in safety or efficacy between younger and older ( $\geq 65$  years of age) patients.
- *Race, ethnicity, and/or gender:* Current clinical experience with sorafenib (Nexavar) and sunitinib (Sutent) has not identified differences in safety or efficacy based on race, ethnicity or gender.

**Conclusion**

Sorafenib (Nexavar) and sunitinib (Sutent) are non-preferred/non-formulary because:

<b>Reason</b>	<b>sorafenib (Nexavar)</b>	<b>sunitinib (Sutent)</b>
Evidence of improved median overall survival  ARCC GIST	No Not applicable	No No
Useful evidence of superiority over existing treatments	No	No
Potential for off-label use	High	High

## Products

Drug Products	FDA approval	FDA approved indications	Usual Dose/Route	Cost <sup>a</sup>	Potential Off-label Uses <sup>b</sup>
aldesleukin (Proleukin <sup>®</sup> ) <sup>1</sup>	05/1992	Treatment of adults with: 1. metastatic renal cell carcinoma (RCC). 2. metastatic melanoma.	600,000 IU/kg IV q8h x 14 doses, 9 days rest, then repeat. 7 week rest period between courses.	\$50,086 <sup>c, d, e</sup>	AML, atopic dermatitis, HIV, basal cell carcinoma, glioma, Kaposi's sarcoma, Epstein-Barr virus infection.
bevacizumab (Avastin <sup>®</sup> ) <sup>2</sup>	02/2004	First-line metastatic carcinoma of the colon or rectum in conjunction with 5-fluorouracil.	10mg/kg IV every two weeks.	\$9,625 <sup>c, d</sup>	Breast cancer, carcinoma of prostate, metastatic RCC, non-small cell lung cancer.
gemcitabine HCl (Gemzar <sup>®</sup> ) <sup>3</sup>	05/1996	First-line treatment of: 1. Metastatic breast cancer. 2. Inoperable, locally advanced (Stage IIIA or IIIB) or metastatic non-small cell lung cancer. 3. Pancreatic cancer (locally advanced stage II or III, or metastatic stage IV).	800 to 1000 mg/m <sup>2</sup> IV on days 1, 8, and 15 of each 28-day cycle.	\$3,072 to \$3,510 <sup>d, f</sup>	Malignant: - Mesothelioma - Neoplasm of adrenal cortex - Neoplasm of soft tissue - Tumor of biliary tract - Tumor of urinary bladder testicular cancer, RCC.
interferon alfa-2a (Roferon-A <sup>®</sup> ) <sup>4</sup>	10/1984	1. Chronic hepatitis C 2. Hairy cell leukemia 3. Chronic myelogenous leukemia (CML).	6 to 18 MIU SQ three times per week.	\$1,112 to \$3,131	AIDS-related KS angiosarcoma, colorectal cancer, HIV infection, liver carcinoma, glioma, melanoma, multiple myeloma (MM), non-Hodgkin's lymphoma, RCC, skin cancer.
interferon alfa-2b (Intron <sup>®</sup> A) <sup>5</sup>	10/1983	1. Chronic hepatitis C 2. Hairy cell leukemia 3. Malignant melanoma 4. Follicular melanoma 5. Condylomata acuminata 6. AIDS-related Kaposi's sarcoma (KS)	10 to 18 MIU SQ/IM three times per week.	\$2,036 to \$3,665	Angioblastoma, breast cancer, CML, liver carcinoma, MM, melanoma, neoplasms of the GI tract, renal cell carcinoma, polycythemia vera.
sorafenib (Nexavar <sup>®</sup> ) <sup>6</sup>	12/2005	Advanced renal cell carcinoma.	400 mg (2 x 200mg) p.o. b.i.d.	\$5,056	Pancreatic cancer, non-small cell lung cancer, melanoma, solid tumors.
sunitinib maleate (Sutent <sup>®</sup> ) <sup>7</sup>	1/2006	1. Gastrointestinal stromal tumor 2. Advanced renal cell carcinoma.	50 mg (1 capsule) p.o. daily; 4 weeks of treatment, followed by 2 weeks off.	\$7,482 (\$4988 if averaged over 3 mo)	Pancreatic cancer, non-small cell lung cancer, melanoma, solid tumors.
imatinib mesylate (Gleevec <sup>®</sup> ) <sup>8</sup>	5/2001	1. Chronic myeloid leukemia (Philadelphia chromosome +) 2. Gastrointestinal stromal tumor	400 mg to 600 mg per day in adults. 260 mg/m <sup>2</sup> /day in children	\$3082 to \$6164	ALL, hypereosinophilic syndrome, Myelofibrosis, Polycythemia vera, Rheumatoid arthritis

<sup>a</sup> Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of March 2006 for 28 days of therapy, unless otherwise specified.

<sup>b</sup> As listed in © 1974 – 2005 Thomson MICROMEDEX database or as referenced.

<sup>c</sup> Based on a 70-kg adult.

<sup>d</sup> Does not include administration costs.

<sup>e</sup> Cost is per 10-week cycle (5 cycles per year).

<sup>f</sup> Based on an adult with BSA = 1.73m<sup>2</sup>.

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