



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

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

February 2008

#### 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 missing significant clinical trials
- 2- Mfg provided all relevant trials; missing pharmacoeconomic model
- 3- Mfg provided all relevant trials and information

#### Executive Summary

Medications:	FDA approved indications:		
	Advanced RCC	GIST (after failure or intolerance to Gleevec)	Advanced HCC
sorafenib (Nexavar)	December 2005	-----	November 2007
sunitinib (Sutent)	January 2006	January 2006	-----

- Both sorafenib (Nexavar) and sunitinib (Sutent) received accelerated FDA approval in advanced RCC and GIST. In granting these approvals, the FDA considered:
  - The limited options and poor survival in patients with advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumor (GIST).
  - Non-randomized clinical trials.
  - Improvements reported in surrogate endpoints (e.g. tumor response) to correlate with a clinical benefit in these patient populations (in lieu of trials that measure overall survival).
- In November 2007, sorafenib (Nexavar) received additional FDA approval in advanced hepatocellular carcinoma (HCC), a disease state for which there are no established treatment options.
- Once started, treatment with sorafenib (Nexavar) or sunitinib (Sutent) is typically continued until there is disease progression or an intolerable adverse effect.
- 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.

*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.

## Executive Summary: Evidence

Table 1: The following summarizes the evidence for sorafenib (Nexavar) and sunitinib (Sutent):

	sorafenib (Nexavar)		sunitinib (Sutent)	
<b>Condition</b>	Advanced HCC	Advanced RCC	Advanced RCC	GIST
<b>Evidence</b>	Reliable	Unreliable	Unreliable	Uncertain clinical usefulness
<b>Study Design</b>	Randomized, placebo-controlled	Randomized, placebo-controlled	Open-label	Randomized, placebo-controlled
<b>Scientific Data Analysis</b>				
- Significant study design flaws		√	√	
- Lack of clinically relevant endpoint (used surrogate markers that do not correlate to overall survival)		√ (PFS)	√ (tumor response)	√ (TTP)
<b>Survival data</b>	Yes	No -- Survival data is pending. However, results will be unreliable do to significant protocol changes that occurred during the trial.	No	No -- Survival reported at 6 months, but is not reliable since placebo patients were given the opportunity to “roll-over” to Sutent after reaching endpoint.
<b>Comparative Head-to-head</b>	No -- There are no other systemic therapies that have shown benefit in HCC	No	Yes -- Open-label, head-to-head trial with interferon.	No -- There are no comparative studies with other therapies in patients resistant to treatment with imatinib mesylate (Gleevec) or treatment-naïve patients.
<b>Adverse Events</b>  Note: Trials were not designed or powered to detect harms. Therefore, harms data are not reliable of evaluating long-term safety.	<ul style="list-style-type: none"> <li>- anorexia</li> <li>- diarrhea</li> <li>- nausea</li> <li>- hand-foot skin reactions</li> <li>- vomiting</li> <li>- alopecia</li> <li>- bleeding</li> </ul>	<ul style="list-style-type: none"> <li>- fatigue</li> <li>- diarrhea</li> <li>- hypertension</li> <li>- nausea</li> <li>- rash or desquamation</li> <li>- hand-foot skin reactions</li> <li>- alopecia</li> </ul>	<ul style="list-style-type: none"> <li>- fatigue,</li> <li>- diarrhea</li> <li>- nausea</li> <li>- mucositis/stomatitis</li> <li>- dyspepsia</li> <li>- altered taste</li> </ul>	<ul style="list-style-type: none"> <li>- fatigue</li> <li>- diarrhea</li> <li>- nausea</li> <li>- anorexia</li> <li>- skin discoloration</li> <li>- vomiting</li> <li>- asthenia</li> <li>- constipation</li> <li>- dysgeusia</li> </ul>

**Decision:**

- Sorafenib (Nexavar) is preferred/formulary because:
  - There is possibly useful evidence that it improves survival in patients with advanced HCC.
  - It is the only treatment option that has shown any benefit in this difficult to treat population.
  
- Sunitinib (Sutent) is non-preferred/non-formulary because:
  - There is no reliable evidence supporting its use in advanced RCC or as a second-line therapy in GIST.
  - Improved progression-free survival (radiographic endpoint) has not been correlated with improved overall survival in advanced RCC.
  - Improved time-to-progression of disease (radiographic endpoint) has not been correlated with improved survival in GIST.

## Products

Drug Products	FDA approval	FDA approved indications	Usual Dose/Route	Potential label Uses <sup>a</sup>	Off-
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.	AML, atopic dermatitis, HIV, basal cell carcinoma, glioma, Kaposi's sarcoma, Epstein-Barr virus infection.	
bevacizumab (Avastin <sup>®</sup> ) <sup>2</sup>	02/2004	1. First-line metastatic carcinoma of the colon or rectum with 5-fluorouracil	10mg/kg IV every two weeks.	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.	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.	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.	Angioblastoma, breast cancer, CML, liver carcinoma, MM, melanoma, neoplasms of the GI tract, renal cell carcinoma, poly-cythemia vera.	
sorafenib (Nexavar <sup>®</sup> ) <sup>6</sup>	12/2005	1. Advanced RCC 2. Advanced hepatocellular carcinoma	400mg (2 x 200mg) p.o. b.i.d.	Pancreatic cancer, non-small cell lung cancer, melanoma, solid tumors.	
sunitinib maleate (Sutent <sup>®</sup> ) <sup>7</sup>	1/2006	1. Gastrointestinal stromal tumor (GIST) 2. Advanced RCC	50mg (1 capsule) p.o. daily; 4 weeks of treatment, followed by 2 weeks off.	Pancreatic cancer, non-small cell lung cancer, melanoma, solid tumors.	
temsirolimus (Torisel <sup>™</sup> ) <sup>23</sup>	5/2007	1. Advanced RCC	25mg infusion qweek (over 30-60 min)	Glioblastoma, melanoma, lymphoma, myeloma	
imatinib mesylate (Gleevec <sup>®</sup> ) <sup>8</sup>	5/2001	1. CML (Philadelphia chromosome +) 2. GIST	400mg to 600mg per day in adults. 260mg/m <sup>2</sup> /day in children	ALL, hypereosinophilic syndrome, Myelofibrosis, Polycythemia vera, Rheumatoid arthritis	

<sup>a</sup> As listed in © 1974 – 2007 Thomson MICROMEDEX database or as referenced.

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