



Therapeutic Class ReviewSM

Antineoplastics – dasatinib (Sprycel[®])

October 2008

New Product for Review:

dasatinib (Sprycel[®]) [Bristol-Myers Squibb]

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)

Executive Summary:

Background on chronic myeloid leukemia (CML):

- CML is a myeloproliferative disorder.
 - The annual incidence rate is 1.6 cases per 100,000 adults.
 - There are approximately 4,600 new cases diagnosed in the U.S. each year.
- The Philadelphia chromosome, which results from a gene translocation, is implicated in the pathogenesis of CML. The Philadelphia chromosome can be identified in 95% of adults with CML.
- CML may occur in the chronic phase, accelerated phase, or blast crisis.
 - The majority of patients are diagnosed with chronic phase CML.
 - Untreated, chronic CML progresses to the more aggressive accelerated and blast phases after 4 to 5 years.
 - Median survival of patients in blast crisis is 6 months.
- Allogeneic stem cell transplantation is the only treatment proven to cure CML, but may not be an option for all patients.^[22]
- Imatinib (Gleevec) is currently the treatment of choice for most newly diagnosed patients with CML.^[22]

Background on Ph + ALL:

- Ph + ALL accounts for approximately 2.3% of all leukemias.
- Ph + ALL results from uncontrolled proliferation and expansion of immature lymphoid cells in the blood, bone marrow, and other organs.
- Imatinib (Gleevec) is the current standard of care. Bone marrow transplantation is the only curative treatment, but carries significant risk.

Treatment of CML and Ph+ ALL:

- Dasatinib (Sprycel) received accelerated approval for the treatment of CML and Ph+ ALL in patients resistant or intolerant to imatinib (Gleevec) in June 2006. ^[1]
- Nilotinib (Tasigna), another multikinase inhibitor, was approved by the FDA in October 2007 for the treatment of chronic and accelerated phases of CML in patients resistant or intolerant to imatinib (Gleevec). It is currently not indicated for Ph+ ALL. ^[14]
- Comparison of FDA-approved indications for tyrosine kinase inhibitors used in CML:

Medication	CML phase			Ph+ALL	MDS	Masto-cytosis	HES/CEL	GIST
	Chronic	Accelerated	Blast					
dasatinib (Sprycel)	X	X	X	X				
imatinib (Gleevec)	X	X	X	X	X	X	X	X
nilotinib (Tasigna)	X	X						

Ph+ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; MDS: myelodysplastic syndromes; HES/CEL: hypereosinophilic syndrome/chronic eosinophilic leukemia; GIST: gastrointestinal stromal tumor

- The efficacy of these medications is based on surrogate endpoints: cytogenetic and hematologic response.
- Cytogenetic response (suppression of the Philadelphia chromosome) is the standard of care when monitoring the clinical progression of CML and Ph+ ALL and has greatly improved survival in these populations relative to historical comparators.
- Both dasatinib (Sprycel) and nilotinib (Tasigna) may be beneficial when there is resistance or intolerance to imatinib (Gleevec).
- Tumor resistance has been reported with all of these agents.
- Current National Comprehensive Cancer Network (NCCN) guidelines place dasatinib (Sprycel) and nilotinib (Tasigna) as second-line agents in the treatment of CML. ^[5]
- Post marketing studies have uncovered reports of cardiotoxicity with imatinib (Gleevec). It is not currently known if this toxicity will also be seen with long-term dasatinib (Sprycel) use.
- Potential off-label uses of dasatinib (Sprycel) include gastrointestinal stromal tumor, myelodysplastic syndrome, cancers of the head and neck, breast, colon, prostate and lung, and melanoma.

Evidence

- There is no useful evidence regarding the efficacy of dasatinib (Sprycel) in the treatment of CML or Ph+ ALL.
 - Trials were of open-label design with no comparator arm.
 - Surrogate endpoints were used (no overall survival data).
 - Preliminary data reported is of short duration (data reported at 12 weeks to 6 months).
- In addition, there is no useful evidence:
 - Comparing the safety and efficacy of nilotinib (Tasigna) with dasatinib (Sprycel) in Ph+ CML.
 - Supporting the efficacy of nilotinib (Tasigna) in patients who have not responded to dasatinib (Sprycel) in the treatment of Ph+ CML.

Decision

Dasatinib (Sprycel) is preferred/formulary because:

- It meets the need for a second-line option for the treatment of CML when imatinib (Gleevec) is not effective or not tolerated.
- Of the two second-line options, dasatinib (Sprycel) has a small advantage over nilotinib (Tasigna) because:
 - There is more clinical experience with dasatinib (Sprycel).
 - It has a longer track record regarding its safety.
 - It is available at a lower cost.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
dasatinib (Sprycel) ⁽¹⁾	6/2006	4/2020	1. Ph+ ALL (resistant to prior therapy) 2. CML, all phases (resistant or intolerant to imatinib [Gleevec])	<i>CML- chronic phase:</i> 100 mg by mouth once daily <i>Other indications:</i> 70 mg by mouth twice daily	Gastrointestinal stromal tumor (GIST), multiple myeloma, chronic lymphocytic leukemia, prostate cancer

imatinib (Gleevec) ^[2]	5/2001	8/2009 7/2015	<ol style="list-style-type: none"> 1. Ph+CML (all phases) 2. Ph+ALL (relapsed or refractory) 3. Myelodysplastic or myeloproliferative diseases w/ PDGFR gene re-arrangements 4. Aggressive systemic mastocytosis (without the c-Kit mutation) 5. Hypereosinophilic syndrome and/or chronic eosinophilic leukemia 6. Unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans 7. Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) 	<p><i>CML- chronic phase:</i> 400 mg to 600 mg PO daily</p> <p><i>CML- accelerated or blastic phase:</i> 600 mg PO daily to 400 mg PO BID</p>	Ph+ALL (newly diagnosed), metastatic melanoma, myelofibrosis, polycythemia vera, rheumatoid arthritis
interferon alfa-2a (Roferon-A) ^[3]	10/1984	n/a (biologic)	<ol style="list-style-type: none"> 1. Chronic myeloid leukemia (Philadelphia chromosome +) 2. Hairy cell leukemia 3. Chronic hepatitis C 	<p><i>CML- chronic phase:</i></p> <p><u>Adults:</u> 9 MIU SQ daily</p> <p><u>Children:</u> 2.5-5 MIU/m² IM daily</p>	AIDS-related Kaposi's sarcoma, angiosarcoma, Behcet's syndrome, cervical cancer, colorectal cancer, condyloma acuminatum, dyserythropoiesis, hepatitis, Japanese encephalitis, glioma, malignant melanoma, multiple myeloma, non-Hodgkin lymphomas, ovarian cancer, renal cell carcinoma
nilotinib (Tasigna) ^[14]	10/2007	7/2023	<ol style="list-style-type: none"> 1. Chronic phase and accelerated phase CML in patients resistant to or intolerant to prior therapy that included imatinib (Gleevec) 	400 mg PO BID [empty stomach]	Blastic phase CML resistant or intolerant to imatinib (Gleevec)
cytarabine (Cytosar-U) ^[4]	12/1998	expired	<ol style="list-style-type: none"> 1. Chronic myeloid leukemia, Blast phase 2. Meningeal leukemia; Treatment and Prophylaxis 3. Acute lymphoid leukemia 4. Acute myeloid leukemia 	Optimal dose not defined	Hodgkin's disease, malignant meningitis, non-Hodgkin's lymphoma, Burkitt's lymphoma, CML, malignant lymphoma, mantle cell lymphoma, microglioma, myelodysplastic syndrome, neoplastic pleural effusion, progressive multifocal leukoencephalopathy, retinoblastoma, small cell carcinoma of the lung

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in Orange Book as of 05/01/08.

^c As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

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