

New Drug Bulletin:**Dasatinib (Sprycel™ - Bristol-Myers Squibb Company)**

October 18, 2006

Written by Winter Chan, PharmD Student

Edited by Shannon Howarth, PharmD, Drug Information Specialist

Dasatinib is an oral chemotherapy agent labeled for the treatment of adults with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who are intolerant of or resistant to prior therapy including imatinib. It acts by inhibiting multiple tyrosine kinases, which ultimately results in inhibition of leukemia cell proliferation.

Maximum plasma concentrations are observed from 30 minutes to 6 hours following dasatinib oral administration. Dasatinib doses ranging from 15 to 240 mg/day demonstrate proportional increases in AUC and linear elimination. Dasatinib's apparent volume of distribution is 2,505 liters, implying that it largely distributes into the extravascular space. Protein binding of dasatinib is 96% and its active metabolite is 93%. Dasatinib is primarily metabolized to its active metabolite via the cytochrome P450 enzyme 3A4. Approximately 5% of dasatinib's AUC can be attributed to the active metabolite. It is eliminated primarily via the feces (85%).

The efficacy and safety of dasatinib was determined in four single-arm multicenter studies in patients with CML or Ph+ ALL who exhibited resistance or intolerance with imatinib. Patients in all phases of CML and Ph+ ALL exhibited cytogenetic and hematologic responses with dasatinib at 12 weeks as shown in Table 1.

Table 1. Efficacy of Dasatinib in Clinical Studies

	Chronic (n = 186)	Accelerated (n = 107)	Myeloid Blast (n = 74)	Lymphoid Blast (n = 42)	Ph+ ALL (n = 36)
Major Hematologic Response, mean (range)	NA	59% (49-68)	32% (22-44)	31% (18-47)	42% (26-59)
Complete Hematologic Response, mean (range)	90% (85-94)	33% (24-42)	24% (15-36)	26% (14-42)	31% (16-48)
Major Cytogenetic Response, mean (range)	45% (37-52)	31% (22-41)	30% (20-42)	50% (34-66)	58% (41-74)
Complete Cytogenetic Response, mean (range)	33% (26-40)	21% (14-30)	27% (17-39)	43% (28-59)	58% (41-74)

In Phase I and II clinical trials in patients with leukemia, the most commonly reported adverse effects included fluid retention (50%), diarrhea (49%), bleeding events (40%), and headache (40%). Potentially serious adverse events included pyrexia (9%), pleural effusion (8%), febrile neutropenia (7%), gastrointestinal bleeding (6%), pneumonia (6%), thrombocytopenia (5%), serious diarrhea (5%), dyspnea (4%), anemia (3%), and cardiac failure (3%). Myelosuppression occurred frequently in all patient populations. Patients exhibiting severe myelosuppression recovered following dose interruption or reduction.

Dasatinib is a CYP3A4 substrate and CYP3A4 inhibitor. Common drug interactions and recommendations are listed in Table 2.

Table 2. Common Drug Interactions with Dasatinib

Drugs		Possible Effects	Recommendations
CYP3A4 Inhibitors	Ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, telithromycin	Increased dasatinib plasma concentrations	Avoid concomitant use.
CYP3A4 Inducers	Dexamethasone, phenytoin, carbamazepine, phenobarbital, rifampin, St. John's wort	Decreased dasatinib plasma concentrations	Use other agents with less enzyme induction.
Antacids	Aluminum hydroxide/magnesium hydroxide		Administer 2 hours apart from the dasatinib dose.
H2 Blockers & PPIs	Famotidine and omeprazole		Concomitant use is not recommended.
CYP3A4 Substrates	Alfentanil, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids	Increased exposure to narrow therapeutic medications	Administer with caution.

The recommended dose for CML and Ph+ ALL is 70 mg orally twice daily with or without a meal. Do not crush or chew dasatinib and take at approximately the same time each day. Increases or decreases of 20 mg per dose are recommended based on safety and tolerability. Table 3 includes available dosage forms and costs for dasatinib and imatinib.

Table 3. Cost Comparison of Dasatinib and Imatinib

	Available Dosage Forms	Dosage Regimen	Average Wholesale Price (30-Day Supply)	Wholesale Acquisition Cost (30-Day Supply)
Dasatinib Sprycel™	20 mg, 50 mg, 70 mg	70 mg twice a day	\$4676.40	\$3897.00
Imatinib Gleevec®	100 mg, 400 mg	400 mg daily	\$3170.40	\$2641.80

In summary, dasatinib is a new oral chemotherapeutic agent for the treatment of chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia patients who have developed resistance or intolerance to prior therapy.

References:

1. Sprycel™ (dasatinib tablets). Princeton, NJ: Bristol-Myers Squibb Company; 2006.
2. Fleming T, ed. 2006 Red Book. Montvale, NJ: Thomson PDR; 2006.

©2006, Department of Pharmacy Services, University of Utah Hospital, Salt Lake City, Utah. For more information, contact the Drug Information Service at 801-581-2073 or drug.info@hsc.utah.edu.