Dasatinib Tablets (Sprycel)

**Manufacturer:** Bristol-Myers Squibb Company, Princeton, NJ

**Indication:** Dasatinib is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast-phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy, including imatinib mesylate (Gleevec, Novartis). The effectiveness of dasatinib is based on hematological and cytogenetic response rates. There have been no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Dasatinib is also indicated for adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy.

**Drug Class:** Dasatinib is an inhibitor of multiple tyrosine kinases. Its chemical name is N-[2-chloro-6-methylphenyl]-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate.

**Uniqueness of Product:** At nanomolar concentrations, dasatinib inhibits the following kinases: breakpoint cluster region–Abelson (Bcr-Abl): Src family (Src, Lck, Yes, Fyn); C-kit; EphA2; and platelet-derived growth factor receptor, beta polypeptide (PDGFR-β). Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the Abl kinase.

In *in vitro*, dasatinib was active in leukemic cell lines representing variants of imatinib-sensitive and imatinib-resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and ALL cell lines overexpressing Bcr-Abl. Under the conditions of the assays, dasatinib overcame imatinib resistance resulting from Bcr-Abl kinase domain mutations, activation of alternate signaling pathways involving the Src family kinases (Lyn, Hck), and multidrug resistance gene overexpression.

**Warnings:**

**Pregnancy (Category D).** Dasatinib may cause fetal harm in pregnant women. In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, fetal toxicity was observed in rats and rabbits and fetal death was observed in rats.

The lowest doses of dasatinib (in rats, 2.5 mg/kg per day or 15 mg/m² per day; in rabbits, 0.5 mg/kg per day or 6 mg/m² per day) resulted in embryo-fetal toxicities. These doses produced maternal area-under-the-curve (AUC) concentrations of 105 ng • hour/ml (0.3-fold the human AUC in females at the recommended dose of 70 mg twice daily) and 44 ng • hour/ml (0.1-fold the human AUC) in rats and rabbits, respectively.

Dasatinib is not recommended for women who are pregnant or who are contemplating pregnancy. If dasatinib is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.

The potential effects of dasatinib on sperm counts, function, and fertility have not been studied. Sexually active men and women taking dasatinib should use adequate contraception.

**Precautions:**

**Myelosuppression.** Treatment with dasatinib is associated with severe grade 3 or 4 thrombocytopenia, neutropenia, and anemia, according to National Cancer Institute Common Toxicity Criteria (NCI CTC). The occurrence of these events is more frequent in patients with advanced CML or Ph+ ALL than in those with chronic-phase CML.

Complete blood counts should be performed weekly for the first two months and then monthly thereafter or as clinically indicated. Myelosuppression was generally reversible and usually managed when the drug was withheld temporarily or when the dose was reduced.

**Bleeding-Related Events.** In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. Severe CNS hemorrhages, including fatalities, occurred in 1% of patients receiving dasatinib. Severe gastrointestinal (GI) hemorrhage occurred in 7% of patients, and treatment and transfusions generally had to be interrupted. Other cases of severe hemorrhage occurred in 4% of patients. Most bleeding events were associated with severe thrombocytopenia.

Patients were excluded from participating in dasatinib clinical studies if they took medications that inhibited platelet function or anticoagulants. Caution should be exercised if patients are required to take these types of medications.

**Fluid Retention.** Dasatinib was associated with fluid retention, which was severe in 9% of patients; pleural effusion was reported in 5% of patients, and pericardial effusion was reported in 1%. Severe ascites, generalized edema, and severe pulmonary edema were each reported in 1% of patients.

Patients who develop symptoms suggestive of pleural effusion, such as dyspnea or dry cough, should be evaluated by chest x-ray. Patients with severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention was typically managed by supportive care measures such as diuretics and short courses of steroids.

**QT Prolongation.** *In vitro* data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (the QT interval). In single-arm clinical studies in patients with...
leukemia who were treated with dasatinib, the mean corrected QT (QTc) interval changes from baseline using Fridericia’s method (QTcF) were 3 to 6 milliseconds (msec); the upper 95% confidence intervals for all mean changes from baseline were less than 8 msec. In nine patients, QTc prolongation was reported as an adverse event. Three patients (fewer than 1%) experienced a QTcF greater than 500 msec.

Dasatinib should be administered with caution to patients who have or who may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medications or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected before dasatinib administration.

**Dosage and Administration:** The recommended dosage of dasatinib is 140 mg/day, administered orally in two divided doses (70 mg twice daily): one dose in the morning and one dose in the evening, with or without a meal. Tablets should not be crushed or cut; they should be swallowed whole.

In clinical studies, treatment with dasatinib was continued until disease progression or until it was no longer tolerated by the patient. The effect of stopping treatment after the achievement of a complete cytogenetic response has not been investigated.

**Commentary:** Dasatinib offers a new treatment option for patients with CML or Ph+ ALL who are resistant or intolerant to prior therapy, including imatinib. Known mechanisms of imatinib resistance include mutations in the protein sequence of the Bcr-Abl tyrosine kinase, multidrug resistance gene overexpression, and the activation of alternate signaling pathways involving the Src family kinases.

For many patients with CML, the risk of developing resistance increases with the number of years of previous treatment and severity of disease. Patients with advanced Ph+ ALL generally develop resistance more rapidly (in about two months) than patients with CML (in 10 months), including those in the blast phase.

Dasatinib is the first approved oral tyrosine kinase inhibitor predicted to bind to multiple conformations of the Abl kinase based on modeling studies. At nanomolar concentrations, dasatinib inhibits Bcr-Abl, Src family, C-kit, EphA2, and PDGFRβ. By targeting these kinases, dasatinib inhibits the overproduction of leukemia cells in the bone marrow of patients with CML and Ph+ ALL, and it enables normal production of red blood cells, white blood cells, and blood platelets to resume.

Imatinib has rightfully been heralded as a breakthrough drug. Dasatinib is an excellent example, though, of how cancer researchers are learning from the successes and failures of targeted therapies like imatinib to make important advances in the development of next-generation targeted agents. Dasatinib has a 325-fold stronger affinity for its gene target, Bcr-Abl, than imatinib does, and it appears to be effective against 18 of the 19 identified mutated forms of Bcr-Abl—the very mutations that drive imatinib resistance.

**Sources:** www.bms.com; www.medpagetoday.com; www.cancer.gov

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**Bevacizumab (Avastin) Plus Intravenous (IV) 5-Fluorouracil Chemotherapy**

**Manufacturer:** Genentech, Inc., South San Francisco, CA

**Indication:** The combination of bevacizumab and 5-fluorouracil (5-FU) is a first-line or second-line treatment for patients with metastatic colon or rectal cancer.

**Drug Class:** Bevacizumab is a therapeutic antibody that is believed to work by targeting and inhibiting the function of a natural protein, vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation, a process known as angiogenesis. In preclinical models, anti-VEGF agents such as bevacizumab may work by causing the following changes in the blood vessels that support tumor growth:

- **regression of existing microvessels:** helping to arrest tumor growth and reduce tumor size
- **normalization of surviving mature vasculature:** making the tumor vasculature more conducive to effective anti-cancer therapy
- **inhibition of vessel growth and neovascularization** (stopping the sprouting of new microvasculature from existing vessels)

5-FU is a commonly used antineoplastic drug to treat cancers of the breast, head and neck, anus, stomach, colon, and some skin cancers. It is a member of the fluoropyrimidine class of anticancer drugs and is part of a group of chemotherapy drugs known as antimetabolites. Antimetabolites are similar to normal body molecules, but they differ slightly in structure. These differences mean that antimetabolites stop cells from working properly instead of helping them. Antimetabolites often prevent cells from making and repairing DNA, which cancer cells need to do in order to grow and multiply. Antimetabolites also inhibit the activities of normal cells.

**Uniqueness of the Combination:** Bevacizumab is the only biologic therapy with a demonstrated survival benefit in colorectal cancer. In combination with 5-FU chemotherapy, it may offer a new option to colorectal cancer patients who have received a previous treatment regimen.

The FDA’s approval was based on a study showing that patients who received bevacizumab plus the 5-FU-based chemotherapy regimen (FOLFOX4 (oxaliplatin/5-FU/leucovorin) had a 25% reduced risk of death (based on a hazard ratio of 0.75). The primary endpoint was equivalent to a 33% improvement in overall survival, compared with patients who received FOLFOX4 alone.

The median survival time for patients receiving bevacizumab plus FOLFOX4 was 13 months. For those patients receiving FOLFOX4 alone, the median survival time was 10.8 months.

**Boxed Warning:**

**Gastrointestinal Perforations.** Bevacizumab can result in the development of GI perforation, in some instances resulting in death. Sometimes associated with intra-abdominal abscess, GI perforation occurred throughout treatment with bevacizumab, and it was not correlated with the duration of exposure.

The incidence of GI perforation (fistula formation, intra-
abdominal abscess) in patients receiving bevacizumab was 2.4%. The typical presentation was reported as abdominal pain associated with constipation and vomiting. GI perforation should be included in the differential diagnosis of patients presenting with abdominal pain who are receiving bevacizumab. Bevacizumab therapy should be permanently discontinued in patients with GI perforation.

Complications of Wound Healing. Bevacizumab can cause wound dehiscence, in some instances resulting in death. Bevacizumab therapy should be permanently discontinued in patients with wound dehiscence who require medical intervention. The appropriate interval between the termination of bevacizumab and subsequent elective surgery required to avoid the risks of impaired wound healing or wound dehiscence has not been determined.

Hemorrhage. Serious, and in some cases fatal, hemoptysis has occurred in patients with non–small-cell lung cancer who have been treated with chemotherapy and bevacizumab. In a small study, the incidence of serious or fatal hemoptysis was 31% in patients with squamous histological features and 4% in patients with adenocarcinoma who were receiving bevacizumab, in contrast to no cases in patients treated with chemotherapy alone. Patients with recent hemoptysis should not receive bevacizumab.

Warnings:

Arterial Thromboembolic Events. Patients receiving the bevacizumab/chemotherapy combination had more arterial thromboembolic events (e.g., cerebral infarction, transient ischemic attacks, myocardial infarction, angina) than patients receiving chemotherapy alone. In some instances, these events were fatal.

In a pooled analysis of randomized, controlled clinical trials involving 1,745 patients, the incidence of arterial thromboembolic events was 4.4% with bevacizumab plus chemotherapy and 1.9% with chemotherapy alone. Fatal outcomes for these events occurred in seven of 963 patients (0.7%) receiving bevacizumab plus chemotherapy and in three of 782 patients (0.4%) receiving chemotherapy alone. The incidence of cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1%) was increased in patients receiving bevacizumab compared with those receiving chemotherapy alone. The relative risk of arterial thromboembolic events was greater in patients 65 years and older (8.5% vs. 2.9%) than in patients younger than age 65 (2.1% vs. 1.4%).

The safety of resuming bevacizumab therapy after resolution of an arterial thromboembolic event has not been studied. Bevacizumab should be discontinued in patients who experience a severe arterial thromboembolic event during treatment.

Hypertension. The incidence of severe hypertension was increased in patients receiving bevacizumab compared with controls. Throughout clinical studies, the incidence of NCI CTC grade 3 or 4 hypertension ranged from 8% to 18%.

Classes of medications used for the management of patients with grade 3 hypertension receiving bevacizumab included angiotensin-converting enzyme (ACE)–inhibitors, beta blockers, diuretics, and calcium-channel blockers. Development or worsening of hypertension can necessitate hospitalization or discontinuation of bevacizumab in up to 1.7% of patients. Hypertension can persist after discontinuation of bevacizumab. Complications can include hypertensive encephalopathy and subarachnoid hemorrhage.

In the postmarketing experience, acute increases in blood pressure associated with initial or subsequent infusions of bevacizumab were reported. Some cases were serious and associated with clinical sequelae.

Bevacizumab should be permanently discontinued in patients with hypertensive crisis and temporarily suspended in patients with severe hypertension that is not controlled with medical management.

Proteinuria. In studies 1 and 3, the incidence of NCI CTC grade 3 and 4 proteinuria, characterized as more than 3.5 g per 24 hours, ranged up to 1.8% in patients treated with bevacizumab. Nephrotic syndrome occurred in five of 1,032 (0.5%) patients receiving bevacizumab in clinical studies. One patient died, and one required dialysis. In three patients, proteinuria decreased in severity several months after discontinuation of bevacizumab. Normalization of urinary protein levels, as assessed by 24-hour urine collections, was not observed in any of the patients after discontinuation of bevacizumab therapy.

The highest incidence of proteinuria was observed in a dose-ranging, placebo-controlled, randomized study of bevacizumab in patients with metastatic renal cell carcinoma, an indication for which bevacizumab is not approved. Twenty-four-hour urine collections were obtained in approximately half of the patients enrolled. Among this group of patients, four of 19 patients (21%) receiving bevacizumab 10 mg/kg every two weeks, two of 14 patients (14%) receiving bevacizumab 3 mg/kg every two weeks, and none of the 15 placebo patients experienced NCI CTC grade 3 proteinuria (above 3.5 g of protein per 24 hours). Bevacizumab should be discontinued in patients with nephrotic syndrome. The safety of continued bevacizumab treatment in patients with moderate-to-severe proteinuria has not been evaluated. In most clinical studies, bevacizumab was interrupted if 2 g or more of proteinuria per 24 hours was present, and it was resumed when proteinuria was less than 2 g per 24 hours. Patients with moderate-to-severe proteinuria, as determined by 24-hour collections, should be regularly monitored until improvement or resolution is observed.

Congestive Heart Failure. Congestive heart failure (CHF), defined as NCI CTC grade 2–4 left ventricular dysfunction, was reported in 22 of 1,032 (2%) patients receiving bevacizumab in clinical studies. The risk of CHF appears to be higher in patients receiving bevacizumab who have received previous or concurrent anthracyclines.

In a controlled study in patients with breast cancer (an unlabeled indication), the incidence of CHF was higher in the bevacizumab/chemotherapy arm than in the chemotherapy-alone arm. CHF occurred in 13 of 299 (4%) patients who received prior anthracyclines or irradiation to the left chest wall. CHF occurred in six of 44 (14%) patients with relapsed acute leukemia (an unlabeled indication) who were receiving bevacizumab and concurrent anthracyclines in a single-arm study.

The safety of continuing or resuming bevacizumab therapy in patients with CHF is unknown. Therapy should be discontinued if symptomatic CHF occurs. In patients who develop symptomatic CHF, continued therapy with bevacizumab should be considered only if the potential clinical benefit outweighs the risk. If bevacizumab is considered appropriate for patients with CHF, the drug should be administered with the lowest possible dose and the lowest possible frequency. The administration of bevacizumab in patients with CHF should be accompanied by appropriate medical management.
in patients with cardiac dysfunction has not been studied.

**Dosage and Administration:** Bevacizumab, used in combination with IV 5-FU-based chemotherapy, is administered as an IV infusion of 5 mg/kg or 10 mg/kg every 14 days until disease progression. It should not be administered as an IV push or as a bolus.

The initial bevacizumab dose should be delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be given over 30 minutes.

Patients receive 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for six weeks every eight weeks) or 5-FU/LV plus bevacizumab (5 mg/kg every two weeks) or 5-FU/LV plus bevacizumab (10 mg/kg every two weeks).

**Commentary:** Colorectal cancer is the second leading cause of cancer deaths in the U.S. The American Cancer Society estimates that nearly 150,000 new cases of colorectal cancer were diagnosed in 2003. Metastatic colorectal cancer, which has spread from its site of origin to distant places in the body, often invades vital organs. Most patients with advanced colorectal cancer are treated not with the intent to cure but with the goal of improving the duration of survival or quality of life.

Bevacizumab is the only biologic therapy with a demonstrated survival benefit in colorectal cancer. In combination with 5-FU, this new indication for metastatic disease offers another option to patients who have received a previous treatment regimen. The addition of bevacizumab to 5-FU/LV as the initial therapy for metastatic colorectal cancer appears to improve survival and progression-free survival more than 5-FU/LV alone.

**Sources:** www.centerwatch.com; www.gene.com; www.pharmacyonesource.com

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**Topotecan HCl Injection (Hycamtin) Plus Cisplatin**

**Manufacturer:** GlaxoSmithKline, Philadelphia, PA

**Indication:** A combination of topotecan and cisplatin is now available for the treatment of advanced (stage 4B) recurrent or persistent carcinomas of the cervix that are not amenable to curative treatment with surgery or radiation.

**Drug Class:** Hycamtin, a semisynthetic derivative of camptothecin, is an antitumor drug with topoisomerase I-inhibitory activity. Its chemical name is (5S)-10-[(dimethyl amino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyran-3’,4’,6,7’ indolizino [1,2-b] quinoline-3,14-(4H,12H)-dione monohydrochloride.

Cisplatin belongs to the group of medications known as alkylating agents. Cisplatin interferes with the growth of cancer cells, which are eventually destroyed. Because the growth of normal body cells may be affected by cisplatin, other effects also occur.

**Uniqueness of Drug:** Topoisomerase I relieves torsional strain in DNA by inducing reversible single-stranded breaks. Topotecan binds to the topoisomerase I–DNA complex and prevents re-ligation of these breaks.

The cytotoxicity of topotecan is thought to be a result of double-stranded DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA.

Mammalian cells cannot efficiently repair these double-stranded breaks. The combination of topotecan and cisplatin is more effective than either agent alone in advanced stage 4B cervical cancer.

**Boxed Warning:** Topotecan HCl for Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Therapy with topotecan should not be given to patients with baseline neutrophil counts below 1,500 cells/mm². To monitor the occurrence of bone marrow suppression, (primarily neutropenia), which may be severe and result in infection and death, health care providers should perform frequent peripheral blood cell counts for all patients receiving topotecan.

Cisplatin can cause a decrease in the number of blood cells in the bone marrow. The physician orders tests before, during, and after treatment to see whether the drug is affecting the blood cells.

Cisplatin can also lead to a severe form of kidney impairment and hearing loss. If patients experience loss of balance, ringing in the ears, trouble hearing, painful urination, or red urine, they should call their doctor immediately. Patients should be advised to keep all of their doctor and laboratory appointments. Laboratory tests are ordered to check the response to cisplatin.

**Warnings:** Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan. Neutropenia is not cumulative over time. The following myelosuppression data are based on:

- the combined experience of 879 patients with metastatic ovarian cancer or small-cell lung cancer who were treated with topotecan monotherapy at a dose of 1.5 mg/m² per day for five days
- the experience of 140 patients with cervical cancer who randomly received topotecan 0.75 mg/m² per day on days one, two, and three, plus cisplatin 50 mg/m² on day one.

**Neutropenia:**

- **Ovarian and small-cell lung cancer experience:** Grade 4 neutropenia (below 500 cells/mm²) was most common during the first course of treatment (60% of patients) and occurred in 39% of all courses, with a median duration of seven days. The nadir neutrophil count occurred at a median of 12 days. Therapy-related sepsis or febrile neutropenia affected 23% of patients, and sepsis was fatal in 1%.
- **Cervical cancer experience:** Grade 3 and 4 neutropenia affected 26% and 48% of patients, respectively.

**Thrombocytopenia:**

- **Ovarian and small cell lung cancer experience:** Grade 4 thrombocytopenia (less than 25,000/mm³) occurred in 27% of patients and in 9% of courses. The median duration was five days, and the median platelet nadir was 15 days. Platelet transfusions were given to 15% of patients in 4% of courses.
- **Cervical cancer experience:** Grade 3 and 4 thrombocytopenia affected 26% and 7% of patients, respectively.
Anemia:
- **Ovarian and small-cell lung cancer experience**: Grade 3 and 4 anemia (less than 8 g/dl) occurred in 37% of patients and in 14% of courses. The median nadir was at day 15. Transfusions were needed in 52% of patients in 22% of courses.
- **Cervical cancer experience**: Grade 3 and 4 anemia affected 34% and 6% of patients, respectively.

**Dosage and Administration:** The following dosing schedule is appropriate: cisplatin 50 mg/m² every three weeks or cisplatin 50 mg/m² on day one and topotecan 0.75 mg/m² IV over 30 minutes for three consecutive days every three weeks.

**Commentary:** Although the death rate from cervical cancer has been dropping steadily since the introduction of the Pap test, the disease is still deadly. The American Cancer Society estimates that 3,700 American women will die of cervical cancer in 2006. Although chemotherapy cannot cure this cancer, it can prolong life and often improve its quality. The new drug combination is a small step along the road to longer and better survival.

Women receiving the topotecan/cisplatin combination lived longer (on average, 9.4 months) than those who received only cisplatin (6.5 months). The combination resulted in more adverse effects (lower blood counts, nausea, and vomiting); however, when the women were asked to assess their quality of life, there was no difference between the two groups.

In summary, adding topotecan to cisplatin lengthened survival in women with advanced cancer of the cervix, although the benefit was small.

**Sources:** [www.gsk.com; www.cancer.org](http://www.gsk.com; www.cancer.org)