In PNH, their most vital organ is exploding.

What will you do?
Chronic hemolysis drives PNH morbidities and mortality.¹

35% of PNH patients die within 5 years of diagnosis.²

Survival of PNH patients compared to controls

• In a patient population in which half the patients have <30% clone, 1 in 7 patients died within 5 years³

→ Reduce chronic hemolysis for optimal PNH management.¹

TARGETING CD30 WITH THE INVESTIGATIONAL ANTIBODY-DRUG CONJUGATE SGN-35

Phase 2 Open-Label Trials of SGN-35 in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) and Systemic Anaplastic Large Cell Lymphoma (ALCL)

Eligible Patients
- Have histologically confirmed CD30-positive disease
- Have FDG-avid disease by PET and measurable disease of at least 1.5 cm by spiral CT
- Have previously received ASCT (HL patients) or front-line chemotherapy (ALCL patients)
- Are ≥12 years old (US sites & ALCL patients at Canadian sites); ≥18 years old (EU sites)

SGN-35 Mechanism of Action
- A CD30-targeted antibody conjugated to the anti-tubulin agent MMAE (an auristatin)
- Selectively induces apoptosis in HL and ALCL cells by binding to CD30, internalizing, and releasing MMAE

Dosing Schedule
- Single IV infusion of SGN-35 on day 1 of each 21-day cycle (up to 16 cycles)

Primary Endpoint
- Overall objective response rate

For more information about these clinical trials and SGN-35
Visit www.clinicaltrials.gov — Trial IDs: NCT00848926 (HL) & NCT00866047 (ALCL) or www.seattlegenetics.com

SGN-35 is an investigational medicine. Safety and efficacy have not been established. There is no guarantee that SGN-35 will become commercially available.
Busulfan is a mutagen and a clastogen. In Carcinogenicity, Mutagenicity, Impairment of Fertility: years). Chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years). Pulmonary: treated in the BUSULFEX (busulfan) Injection clinical trials experienced cardiac tamponade. Cardiac tamponade has been reported in pediatric patients with thalassemia (8/400 or 2% in one series). Other: busulfan can cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been observed in lymph nodes, parathyroid glands, liver, lungs and bone marrows. This cytologic dysplasia may be severe enough to cause difficulty in the interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix. ADVERSE REACTIONS Dimethylacetamide (DMA), the solvent used in the BUSULFEX formulation, was studied in 1962 as a potential cancer chemotherapy drug. In a Phase 1 trial, the maximum tolerated dose (MTD) was 14.8 g/m² for four days. The dose-limiting toxicities in the Phase 1 study were hepatotoxicity as evidenced by increased liver transaminase (SGOT) levels and neurological symptoms as evidenced by hallucinations. The hallucinations had a pattern of onset at one day post completion of DMA administration and were associated with EEG changes. The lowest dose at which hallucinations were recognized was equivalent to 1.9 times that delivered in a typical conditioning regimen using BUSULFEX 0.8 mg/kg for six times 1.6 doses. Other neurological symptoms included somnolence, lethargy, and confusion. The relative contribution of DMA and/or other concomitant medications to neurologic and hepatic toxicities observed with BUSULFEX is difficult to assess. Treatment with BUSULFEX at the recommended dose and schedule will result in profound myelosuppression in 100% of patients, including granulocytopenia, thrombocytopenia, anemia, or a combined loss of formed elements. Adverse reaction information is primarily derived from the clinical study (N=61) of BUSULFEX and the data obtained for high-dose oral busulfan conditioning in the setting of randomized, controlled trials identified through a literature review.

**BUSULFEX Clinical Trials**: In the BUSULFEX (busulfan) injection allogeneic stem cell transplantation clinical trial, all patients were treated with BUSULFEX 0.8 mg/kg as a two-hour infusion every six hours for 16 doses over four days, combined with cyclophosphamide 60 mg/kg x 2 days. Ninety-three percent (95%) of evaluable patients receiving this dose of BUSULFEX maintained an AUC less than 1,500 µM x h for dose 9, which generally corresponds to the AUC that minimizes the risk of HVOD. The most frequent serious consequence of treatment with BUSULFEX at the recommended doses and schedule will result in profound myelosuppression in 100% of patients. The following warnings pertain to different physiologic effects of BUSULFEX in the setting of allogeneic transplantation. Hematopoietic stem cell transplantation. Impairment of pregnancy. Table 1: Summary of the Incidence (±20%) of Non-Hematologic Adverse Events through BMT Day +28 in Patients who Received BUSULFEX Prior to Allogeneic Hematopoietic Progenitor Cell Transplantation

**Drug Interactions**: Itraconazole decreases busulfan clearance by up to 25%, and may produce an AUC ≥ 150 µM x h in some patients. Fluconazole, and the 5-HT3 antagonists ondansetron (Zofran) and granisetron (Kytril) have all been used with BUSULFEX® (busulfan). Phenylalanine decreases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione- transferase. Since the pharmacokinetics of BUSULFEX were studied in patients treated with phenytoin, the clearance of BUSULFEX at the recommended dose may be lower and exposure (AUC) higher in patients not treated with phenytoin. Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (<72 hours) or concomitant with BUSULFEX may result in reduced busulfan clearance based upon the known property of acetaminophen to decrease plasma levels of the blood and tissues.

Pregnancy: Pregnancy Category D. See WARNINGS. Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because an adequate and well-controlled study has not been done in infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
The following sections describe clinically significant events occurring in the BUSULFEX® (busulfan) clinical trials.

**Hematologic:** At the indicated dose and schedule, BUSULFEX produced profound myelosuppression in 100% of patients. Following hematopoietic progenitor cell infusion, recovery of neutrophil counts to ≥5000 cells/mm³ occurred at median day 13 when prophylactic G-CSF was administered to the majority of participants on the study. The median number of platelet transfusions per patient on study was 6, and the median number of red blood cell transfusions on study was 4. Prolonged prothrombin time was reported in one patient (2%).

**Gastrointestinal:** Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Gastrointestinal events were severe in 15% of patients. Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting occurred in 95% through BMT Day +28; nausea was severe in 7%. The incidence of vomiting during BUSULFEX administration (BMT Day 0–7) was 43% in the allogeneic clinical trial. Grade 3-4 emesis developed in 26% of the participants, and Grade 3 nausea in 2 patients. Grade 3 vomiting occurred in 2 patients (4%) and was considered severe in 2%.

**Hepatic:** Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Based on clinical examination and laboratory findings, hepatic veno-occlusive disease was diagnosed in 15% (81/547) of patients treated with BUSULFEX in the setting of conditioning prior to hematopoietic transplantation, was fatal in 2 cases (4%), and yielded an overall mortality from HVOD in the complete complicity of 26% (137 of 547). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones criteria. Fifty-one percent (51%) of patients experienced one or more episodes of infection. Pneumonia was fatal in one patient (2%) and life-threatening in 3% of patients. Fever was reported in 80% of patients; it was mild or moderate in 78% and severe in 3%. Forty-six percent (46%) of patients experienced jaundice. Hyperglycemia was observed in 67% of patients and Grade 3 or 4 hyperglycemia was reported in 5%.

**Cardiovascular:** Mild or moderate tachycardia was reported in 44% of patients. In 7 patients (11%) it was first reported during BUSULFEX administration. Other rhythm abnormalities, which were all mild or moderate, included atrial fibrillation (1%), atrial flutter (2%), ventricular extrasystoles (2%), and third degree heart block (2%). Mild or moderate thrombosis occurred in 33% of patients, and all episodes were associated with the central venous catheter. Hypertension was reported in 36% of patients and was Grade 3/4 in 7%. Mild vasodilation (flushing and warmth) or urticaria was reported in 25% of patients. Other cardiovascular events included cardiomyopathy (5%), mild ECG abnormality (2%), Grade 3 left-sided heart failure in one patient (2%), and moderate pericardial effusion (2%). These events were reported primarily in the pre-cyclophosphamide phase.

**Pulmonary:** Mild or moderate dyspnea occurred in 25% of patients and was severe in 2%. One patient (2%) experienced severe hypoxemia and was intubated. Twenty-eight days after transplantation and was considered life-threatening in 5% of these patients. Hypoxemia was attributed to graft-versus-host disease in six patients and with hepatic veno-occlusive disease in 5 patients. Grade 3-4 SGPT elevations occurred in 7% of patients. Mild or moderate constipation occurred in 38% of patients; ileus developed in 8% and was severe in 2%. Forty-four percent (44%) of patients reported mild or moderate dyspnea. Two percent (2%) of patients experienced mild hematemesis. Pancreatitis developed in 2% of patients. Mild or moderate dysphagia developed in 24% of patients. Severe anorexia was noted in 21% of patients and was mild or moderate in 64%.

**Metabolic:** Hyperglycemia was observed in 67% of patients and Grade 3 hyperglycemia was reported in 15%. Hypermagnesemia was mild or moderate in 77% of patients; hypokalemia was mild or moderate in 62% and severe in 2%; hypocalcemia was mild or moderate in 46% and severe in 3%; hypophosphatemia was mild or moderate in 17%; and hypomagnesemia was reported in 2%. Other reported mild or moderate events included hypothyroidism (mild or moderate 64%, severe 5%), abdominal pain (mild or moderate 69%, severe 3%), asthenia (mild or moderate 49%, severe 2%), unspecified pain (mild or moderate 43%, severe 2%), allergic reaction (mild or moderate 24%, severe 2%), injection site inflammation (mild or moderate 22%), injection site pain (mild or moderate 15%), chest pain (mild or moderate 26%), back pain (mild or moderate 23%), myalgia (mild or moderate 16%), arthralgia (mild or moderate 13%), and ear disorder in 3%.

**Malignancy:** There were two deaths through BMT Day +28 in the allogeneic transplant setting. There were an additional six deaths BMT Day +29 through BMT Day +100 in the allogeneic transplant setting. There were two deaths in the allogeneic transplant setting. There were two deaths through BMT Day +29 in the allogeneic transplant setting. There were two deaths through BMT Day +28 in the allogeneic transplant setting. There were an additional six deaths BMT Day +29 through BMT Day +100 in the allogeneic transplant setting.
For use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation (HSCT) for chronic myelogenous leukemia (CML)

Important Safety Information
At the recommended dosage, IV Busulfex produced profound myelosuppression in all patients (ie, severe granulocytopenia, thrombocytopenia, anemia, or a combination thereof). Frequent complete blood counts should be monitored during treatment and until recovery. Hepatic veno-occlusive disease was diagnosed in 5/61 patients and was fatal in 2/5 cases. Anticonvulsant prophylactic therapy should be administered prior to treatment. Caution should be exercised in patients with a history of seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs. Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious condition following chronic busulfan therapy. Women of childbearing potential should be advised to avoid becoming pregnant as busulfan may cause fetal harm.

The most common nonhematologic adverse events were nausea (92% mild/moderate, 7% severe), stomatitis (71% grade 1–2, 26% grade 3–4), vomiting (95% mild/moderate), anorexia (64% mild/moderate, 21% severe), diarrhea (75% mild/moderate, 5% grade 3–4), insomnia (83% mild/moderate, 1% severe), and fever (78% mild/moderate, 3% life-threatening).

WARNING: BUSULFEX (busulfan) injection is a potent cytotoxic drug that causes profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in allogeneic hematopoietic stem cell transplantation, the use of cancer chemotherapeutic drugs, and the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available. SEE “WARNINGS” SECTION OF FULL PRESCRIBING INFORMATION FOR INFORMATION REGARDING BUSULFAN-INDUCED PANCYTOPENIA IN HUMANS.

Learn more by visiting www.IVBUSULFEX.com

Please see brief summary of prescribing information on the adjacent pages.

*Target value of <1500 μM·min.
1. Package insert for IV Busulfex (busulfan) Injection.
© 2008 Otsuka America Pharmaceutical, Inc.
October 2008 0608A-0127E

Otsuka America Pharmaceutical, Inc.
Rockville, MD 20850

Outcomes through accuracy

- Predictable pharmacokinetics1,2
  93% of patients (55/59) maintained AUC values below the target value* with no dose adjustment
- Established survival1,2
  70% of patients (43/71) were alive at a median follow-up of 288 days post-transplant
- 100% engraftment1,2
  All evaluable patients (60/60) engrafted at a median of 13 days
- Low incidence of severe toxicities1,2
  100% of patients (61/61) completed the 16-dose regimen
- Straightforward IV administration

Learn more by visiting www.IVBUSULFEX.com
Because you want to be completely sure of your samples before you move forward. Because the 2100 Bioanalyzer saves time and money with faster results and fewer repeat experiments. Because better quality control now means better data later. And because confidence in your results is reason enough to choose Agilent.

**How.**

With the Agilent 2100 Bioanalyzer and its RIN algorithm, to ensure the integrity of your RNA samples. With an easy-to-use platform delivering a standardized integrity assessment for total RNA, mRNA, and miRNA. With speed, for high-throughput analysis of 1 μL samples down to 50pg/μL RNA. And most importantly, with confidence that your results will be reproducible.

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Because you want to be completely sure of your samples before you move forward. Because the 2100 Bioanalyzer saves time and money with faster results and fewer repeat experiments. Because better quality control now means better data later. And because confidence in your results is reason enough to choose Agilent.

**WE MAKE IT. You make it happen.**

Visit us at opengenomics.com/bioanalyzer
TOGETHER, WE CARE
CELEBRATING WORLD HEMOPHILIA
DAY APRIL 17, 2009

THE GAP BETWEEN THE DEVELOPED AND DEVELOPING WORLD IS BEGINNING TO CLOSE.

The World Federation of Hemophilia’s Global Alliance for Progress (GAP) supports hemophilia treatment and care across the world:

- Diagnosis rates, as well as levels of access to hemophilia treatment and care, vary greatly in different parts of the world.
- In an effort to address this imbalance, the World Federation of Hemophilia, with Baxter as the founding and leading sponsor, started the Global Alliance for Progress (GAP) in 2003.
- The goal of the GAP programme is to greatly increase the diagnosis and treatment of people with hemophilia in developing countries.

VISIT WWW.WHF.ORG/WHD TO VIEW THE NEW “TOGETHER, WE CARE” EDUCATIONAL VIDEO PODCAST.
When Treating Your Patients:

- Evaluate for other treatable etiologies of anemia (iron, folate, or B₁₂ deficiency, hemolysis, or bleeding) to treat appropriately
- PROCRIT therapy should not be initiated at hemoglobin (Hb) levels ≥10 g/dL
- The dose of PROCRIT should be titrated for each patient to achieve and maintain the lowest Hb level sufficient to avoid the need for red blood cell (RBC) transfusion
- The rate of Hb increase should not exceed 1 g/dL in any 2-week period
- Monitor Hb weekly until stable, and then regularly during therapy
PROCRIT Indication

PROCRIT is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on studies that have shown a reduction in the need for RBC transfusions in patients with metastatic, non-malignant malignancies receiving chemotherapy for a minimum of 2 months. Studies to determine whether PROCRIT increases mortality or decreases progression-free/recurrence-free survival are ongoing.

- PROCRIT is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive chemotherapy.
- PROCRIT is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure due to the absence of studies that adequately characterize the impact of PROCRIT on progression-free and overall survival (see WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence).
- PROCRIT is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding (see PRECAUTIONS: Lack or Loss of Response).
- PROCRIT use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

Important Safety Information

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE

Renal failure: Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

Cancer:
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).
- To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.
- Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

Perisurgery: PROCRIT® (Epoetin alfa) increased the rate of deep venous thromboses in patients not receiving prophylactic anticoagulation. Consider deep venous thrombosis prophylaxis.

Contraindications

- PROCRIT is contraindicated in patients with uncontrolled hypertension or with known hypersensitivity to albumin (human) or mammalian cell-derived products.

Additional Important Safety Information

- Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events (including myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis) when administered ESAs to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies; these risks also increased in controlled clinical trials of patients with cancer. A rate of hemoglobin rise of >1 g/dL over 2 weeks may contribute to these risks.
- PROCRIT therapy should not be initiated at hemoglobin levels ≥10 g/dL.
- The dose of PROCRIT should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion.
- When the hemoglobin reaches a level needed to avoid transfusion or increases by more than 1 g/dL in a 2-week period, the PROCRIT dose should be reduced by 25%. Withhold the dose of PROCRIT if the hemoglobin exceeds a level needed to avoid transfusion. Restart dose at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required. Discontinue if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required.
- Monitor hemoglobin regularly during therapy, weekly until hemoglobin becomes stable.
- Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with PROCRIT; predominately in patients with chronic renal failure receiving PROCRIT by subcutaneous administration. If any patient develops a sudden loss of response to PROCRIT, accompanied by severe anemia and low reticulocyte count, and anti-erythropoietin antibody-associated anemia is suspected, withhold PROCRIT and other erythropoietic proteins. Contact ORTHO BIOTECH (1-888-2ASKOBI or 1-888-227-5526) to perform assays for binding and neutralizing antibodies. If erythropoietin antibody-mediated anemia is confirmed, PROCRIT should be permanently discontinued and patients should not be switched to other erythropoietic proteins.
- The safety and efficacy of PROCRIT therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (e.g., sickle cell anemia, myelodysplastic syndromes, or hereditary spherocytosis).
- In some female patients, menses have resumed following PROCRIT therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.
- Prior to and regularly during PROCRIT therapy monitor iron status; serum ferritin should be >200 ng/mL. During therapy absolute or functional iron deficiency may develop and all patients will eventually require supplemental iron to adequately support erythropoiesis stimulated by PROCRIT.
- Treatment of patients with grossly elevated serum erythropoietin levels (e.g., >200 mUnits/mL) is not recommended.
- During PROCRIT therapy, blood pressure should be monitored carefully and aggressively managed, particularly in patients with an underlying history of hypertension or cardiovascular disease.
- Seizures in PROCRIT-treated patients have been reported in the context of a significant increase in hemoglobin from baseline; increases in blood pressure were not always observed; and patients may have had other underlying central nervous system pathology.
- The most commonly reported side effects (>10%) for PROCRIT in clinical trials were pyrexia, diarrhea, nausea, vomiting, edema, asthenia, fatigue, shortness of breath, paresthesia, and upper respiratory infection.

Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent page.
PROCRIT® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical 
   (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 
   red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without 
   estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in 
   mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 
   women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or 
   a randomized controlled study (referred to as Cancer Study 1 - the 'BEST' study) with another ESA in 939 
   Increased mortality was also observed in a randomized placebo-controlled study of PROCRIT® in adult patients 
   smoking history, even among patients randomized to darbepoetin alfa versus no-treatment (Cancer Studies 5 and 6), in patients receiving chemotherapy for metastatic 
   Erythropoiesis-stimulating agents resulted in decreased locoregional progression-free survival and/or 
   Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 
   treated patients with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following 
   Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was 
   randomized controlled study of PROCRIT® in adult patients with advanced non-small cell lung cancer receiving only 
   Proportion of patients achieving a hematocrit response

<table>
<thead>
<tr>
<th>Cancer Study</th>
<th>Hemoglobin Target (Median 01.02)</th>
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<tr>
<td>Epoetin alfa</td>
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<td>Placebo</td>
<td>12.1 g/dL</td>
<td>Overall survival and locoregional control</td>
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**WARNINGS**

**Risk in Premature Infants**

The multiuse preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

**CONTRAINDICATIONS**

PROCRIT® is contraindicated in patients with:

1. Uncontrolled hypertension. 2. Known hypersensitivity to human erythropoietin.

**INDICATIONS AND USAGE**

PROCRIT® is indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy based on evidence that it have shown a reduction in the need for RBC transfusions in patients with metastatic, non-myeloid malignancies receiving chemotherapy for a minimum of 2 months. Studies to determine whether PROCRIT® increases mortality or decreases progression-free/recovery-free survival are ongoing.

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Decreased locoregional control: Cancer Study 6 (JAHANIA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck. Eighteen percent of treated patients demonstrated a decrease in the rate of locoregional control versus placebo. A decrease in the rate of locoregional control was observed in patients with concurrent radiation therapy and concomitant use of PROCRIT® and other chemotherapeutic agents. A decrease in the rate of locoregional control was noted in patients treated with PROCRIT® for 14 days. In patients with an excessive hematopoietic response, reduce the PROCRIT® dose in accordance with the recommendations described in DOSAGE AND ADMINISTRATION in full Prescribing Information.]

2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with PROCRIT® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 1.2% (n = 2/168) of safety-evaluable patients treated with PROCRIT® and 3.6% (n = 6/165) (p = 0.44) of placebo-treated patients had clinical or asymptomatic thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hematognin increase and the occurrence of clinical events was not significant. Significant thrombotic events could not be evaluated due to the limited schedule of hematoglogin measurements in this study.

The safety and efficacy of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study that enrolled 222 anemic patients ages 5 to 18 receiving treatment for a variety of childhood malignancies. Due to the study design (small sample size and the heterogeneity of the underlying malignancies and of anti-neoplastic treatments employed), a determination of the effect of PROCRIT® on the incidence of these events could not be performed. In the PROCRIT® arm, the overall incidence of thrombotic events was 10.8% and the incidence of serious or life-threatening events was 7.2%.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erthropoietin, in association with PICA or severe anemia (with or without other cytopenias), have been reported in patients receiving PROCRIT® (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 6.0% (n = 10/168) of safety-evaluable patients treated with PROCRIT® and 3.6% (n = 6/165) (p = 0.44) of placebo-treated patients had clinical or asymptomatic thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hematoglogin increase and the occurrence of clinical events was not significant. Significant thrombotic events could not be evaluated due to the limited schedule of hematoglogin measurements in this study.

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DOSAGE AND ADMINISTRATION

IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events.

Prior to initiating treatment with PROCRIT®, a hemoglobin should be obtained to establish that it is >10 to ≤13 g/dL. The recommended dose of PROCRIT® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg PROCRIT® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with PROCRIT® and should continue throughout the course of therapy. Deep venous thrombosis prophylaxis should be strongly considered (see BOXED WARNINGS).

PREPARATION AND ADMINISTRATION OF PROCRIT®

1. Do not shake. It is not necessary to shake PROCRIT®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.

2. Protect the solution from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing PROCRIT®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.

4. Single-dose: 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8°C after initial entry and between doses. Discard 21 days after initial entry.

5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free PROCRIT® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of PROCRIT® containing benzyl alcohol.

Manufactured by:
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One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Distributed by:
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Raritan, New Jersey 08869-0670

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Important Safety Information
RiaSTAP™, Fibrinogen Concentrate (Human), is indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. RiaSTAP™ is not indicated for dysfibrinogenemia.

RiaSTAP™ was approved using maximum clot firmness (MCF) as a surrogate marker likely to predict clinical benefit. Thus, the hemostatic efficacy of RiaSTAP™ in acute bleeding episodes has not been established. A post-marketing study is being conducted to verify clinical endpoints.

RiaSTAP™ is contraindicated in individuals who have manifested severe immediate hypersensitivity reactions, including anaphylaxis, to RiaSTAP™ or its components.

Monitor patients for early signs of allergic or hypersensitivity reactions and if necessary, discontinue administration and institute appropriate treatment. Thrombotic events have been reported in patients receiving RiaSTAP™.

RiaSTAP™ is made from pooled human plasma. Products made from human plasma may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most serious adverse reactions that have been reported in subjects in clinical studies who received RiaSTAP™ are thromboembolic episodes, including myocardial infarction and pulmonary embolism, and allergic-anaphylactic reactions. The most common adverse reactions observed are allergic reactions, including chills, fever, nausea, and vomiting. Monitor patients for early signs of allergic or hypersensitivity reactions and if necessary, discontinue administration.

FINALLY—the access and convenience you’ve been waiting for

- Concentrated lyophilized protein that is easily reconstituted in minutes
- Labeled fibrinogen content to assist with coagulation management
- Demonstrated ability to effectively raise fibrinogen levels to within target levels
- Concentrated fibrinogen allows for low infusion volume\(^1\) and quick administration
- Virus inactivation/removal reduces risk of exposure to infectious agents
- Easily stored and accessed when needed, due to room temperature storage and 30-month shelf life

For more information, visit www.riastap.com.

Please see brief summary of prescribing information on next page.


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1 INDICATIONS AND USAGE

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4 CONTRAINDICATIONS

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5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Allergic reactions may occur. If symptoms of allergic or early signs of hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) occur, immediately discontinue administration (see Patient Counseling Information [17.1]). The treatment required depends on the nature and severity of the reaction.

5.2 Thrombosis

Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Thromboembolic events have been reported in patients treated with RiaSTAP. Weigh the benefits of RiaSTAP administration versus the risk of thrombosis. Patients receiving RiaSTAP should be monitored for signs and symptoms of thrombosis. (see Patient Counseling Information [17.2])

5.3 Transmissible Infectious Agents

RiaSTAP is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and the Creutzfeldt-Jakob disease agent [CJD]) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by a process demonstrated to inactivate or remove certain viruses during manufacturing. (see Description [11]). Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products (see Patient Counseling Information [17.2]). All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-866-915-6958.

6 ADVERSE REACTIONS

The most serious adverse reactions that have been reported in clinical studies or through postmarketing surveillance following RiaSTAP treatment are allergic-anaphylactic reactions and thromboembolic episodes, including myocardial infarction, pulmonary embolism, deep vein thrombosis, and arterial thrombosis.

The most common adverse reactions that have been reported in clinical studies or through postmarketing surveillance following RiaSTAP treatment are allergic reactions and generalized reactions such as chills, fever, nausea, and vomiting.

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in practice.

The most common adverse reactions observed in more than one subject in clinical studies (frequency >1%) were fever and headache.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Adverse reactions reported in patients receiving RiaSTAP for treatment of fibrinogen deficiency include allergic-anaphylactic reactions (including rash, dyspnea, etc.), general reactions such as chills, fever, nausea, vomiting and thromboembolic complications such as myocardial infarction, pulmonary embolism, and deep vein thrombosis.

The following adverse reactions, identified by system organ class, have shown a possible causal relationship with RiaSTAP:

- Allergic-anaphylactic reactions: anaphylaxis, dyspnea, rash
- Cardiovascular: thromboembolism, pulmonary embolism (see Warnings and Precautions, Thrombosis [5.2])
- General/Body as a Whole: chills, fever, nausea, vomiting

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with RiaSTAP. It is not known whether RiaSTAP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RiaSTAP should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

RiaSTAP has not been studied for use during labor and delivery.

8.3 Nursing Mothers

RiaSTAP has not been studied in nursing mothers with congenital fibrinogen deficiency.

8.4 Pediatric Use

RiaSTAP studies have included subjects below the age of 16 years. In the pharmacokinetic study (see Pharmacokinetics [12.3]), 2 children (8 and 11 years), 3 adolescents (12, 14 and 16 years), were studied. Subjects less than 16 years of age (n = 4) had shorter half-life (69.9 ± 8.5h) and faster clearance (0.7 ± 0.1 mg/L) compared to adults (half-life: 82.3 ± 20.0h, clearance: 0.53 ± 0.1 mg/L). The number of subjects less than 16 years of age in this study limits statistical interpretation.

8.5 Geriatric Use

The safety and efficacy of RiaSTAP in the geriatric population has not been studied. There were an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.
publishers to improve compliance with the current NIH public access policy while maintaining the publisher-mandated access embargoes. The pilot project will provide NIH with final articles representing NIH-funded research for an internal use archive at NIH. ASH believes the PMC (NIH Portfolio) Archive program provides a better alternative for authors and journals than a mandated policy with a shorter embargo period. During implementation of this program over the course of the year, ASH hopes to continue to work with the NIH on ways to enhance access.

ASH has implemented a public access policy in which Howard Hughes Medical Institute funded papers are deposited into PMC on payment of a public access fee of $2,000, in addition to the regular publication fees charged to authors. This public access option has now been extended to any author, for the same public access fee of $2,000. Upon payment of the fee, Blood will deposit the article into PMC and ensure immediate free access on the Blood website. Authors can find more information about the public access policy for Blood during the manuscript submission process.

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Get full details or register today at [www.hematology.org](http://www.hematology.org).
GLEEVEC® (imatinib mesylate) tablets are indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome–positive chronic myeloid leukemia (Ph+ CML) in the chronic phase. Follow-up is limited to 5 years.

*As published by Time, Inc., GLEEVEC, in addition to inhibiting Bcr-Abl, is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events.*

---

**Important Safety Information**

- Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking GLEEVEC tablets and to avoid breast-feeding while taking GLEEVEC tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking GLEEVEC should use adequate contraception. If the patient does become pregnant while taking GLEEVEC, the patient should be advised of the potential hazard to the fetus.

- Severe (NCI Grades 3/4) lab abnormalities—including neutropenia (3.6%–48%), anemia (1%–42%), thrombocytopenia (<1%–33%), and hepatotoxicity (approx 5%)—and severe adverse experiences (NCI Grades 3/4), including severe fluid retention (eg, pleural effusion, pulmonary edema, and ascites) and superficial edema (1.3%–11%), hemorrhage (1.8%–19%), and musculoskeletal pain (2%–9%) were reported among patients receiving GLEEVEC®. Severe fluid retention appears to be dose-related, was more common in the advanced phase studies (where the dosage was 600 mg/day), and is more common in the elderly.

- Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

- Dose adjustments may be necessary due to hepatotoxicity, other nonhematologic adverse reactions, or hematologic adverse reactions. Therapy with GLEEVEC was discontinued for drug-related adverse reactions in 2.4% to 5% of patients. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2–3 months).

- A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

- Patients should be weighed and monitored regularly for signs and symptoms of edema, which can be serious or life-threatening. There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure, papilledema, and gastrointestinal (GI) perforation.

- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction occurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

- Consider potential toxicities—specifically liver, kidney, and cardiac toxicity, and immunosuppression from long-term use.
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SURVIVAL: THE NEW BENCHMARK IN CHRONIC PHASE Ph+ CML

GLEEVEC gives the gift of 89% estimated overall survival at 5 years in IRIS (95% CI: 86-92)\(^1\)^

- Estimated overall survival rate in the interferon-alpha (IFN-\(\alpha\)) arm at 5 years was 85.6% (95% CI: 82-89). This end point may be affected by the high crossover rate from IFN-\(\alpha\) to GLEEVEC.\(^1\)^

**The primary efficacy end point of the study was progression-free survival (PFS)**
- GLEEVEC: 83.2% PFS in Ph+ CML in the chronic phase (95% CI: 79-87)
- PFS in the IFN-\(\alpha\) arm at 60 months was significantly lower at 64.1% (95% CI: 59-69) (\(P=0.0001\))

IRIS: International Randomized study of Interferon and STI571 (GLEEVEC 400 mg QD). IRIS is a randomized, open-label multicenter phase III study of 1106 adult patients with newly diagnosed, previously untreated Ph+ CML in the chronic phase. Patients were randomized to receive either GLEEVEC (\(n=553\)) or IFN-\(\alpha\) plus cytarabine (\(n=553\)) as initial treatment. The primary efficacy end point of the study was PFS. Progression was defined as any of the following events: progression to accelerated phase or blast crisis, death, loss of complete hematologic response (CHR) or major cytogenetic response, or in patients not achieving a CHR, an increasing white blood cell count despite appropriate therapeutic management.\(^1\)^

\(^{1}\)Overall survival among adult patients treated with first-line GLEEVEC based on an intent-to-treat analysis (\(N=553\)).

- GLEEVEC is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Dosage of GLEEVEC should increase by at least 50%, and clinical response should be carefully monitored, in patients receiving GLEEVEC with a potent CYP3A4 inducer such as rifampin or phenytoin. Examples of commonly used drugs that may significantly interact with GLEEVEC include ketocnazole, acetaminophen, warfarin, erythromycin, and phenytoin. (Please see full Prescribing Information for other potential drug interactions)
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron

**Common Side Effects of GLEEVEC Tablets**
- The majority of adult Ph+ CML patients who received GLEEVEC in clinical studies experienced adverse reactions at some time, but most were mild to moderate in severity. The most frequently reported adverse reactions (all Grades) were superficial edema (60%-74%), nausea (50%-73%), muscle cramps (28%-62%), vomiting (23%-58%), diarrhea (43%-57%), musculoskeletal pain (38%-49%), and rash and related terms (36%-47%)*
- Supportive care may help management of some mild-to-moderate adverse reactions so that the prescribed dose can be maintained whenever possible. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation. GLEEVEC tablets should not be taken with grapefruit juice and other foods known to inhibit CYP3A4
- Patients should be informed to take GLEEVEC exactly as prescribed, not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

*Numbers indicate the range of percentages in 4 studies among adult patients with Ph+ CML in blast crisis, accelerated phase, and chronic phase.

**References:**
1. GLEEVEC\(^{\text{TM}}\) (imatinib mesylate) tablets prescribing information, East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2007.
Gleevec®
(imatinib mesylate)
Tablets
Rx only

BRIEF SUMMARY: The following information refers to adult patients newly diagnosed with Ph+ CML in chronic phase, unless otherwise noted. Experience with other indications may differ. Please see package insert for full prescribing information.

INDICATIONS AND USAGE
Gleevec® (imatinib mesylate) tablets are indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Follow-up is limited to 5 years.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS

Pregnancy: Category D
Women of childbearing potential should be advised to avoid becoming pregnant while taking GLEEVEC. Sexually active female patients taking GLEEVEC should use adequate contraception.

Gleevec can cause fetal harm when administered to a pregnant woman. Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day (based on body surface area). Teratogenic effects included exomphalos or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum Days 0 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤30 mg/kg (one-third the maximum human dose of 800 mg).

There are no adequate and well-controlled studies with GLEEVEC in pregnant women. Women should be advised not to become pregnant while taking GLEEVEC. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Fluid Retention and Edema: Gleevec is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher GLEEVEC dose and age ≥65 years in the CML studies. Severe peripheral edema was reported in 1.5% of newly diagnosed CML patients taking GLEEVEC and in 2%-6% of other adult CML patients taking GLEEVEC. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking GLEEVEC and in 2%-6% of other adult CML patients taking GLEEVEC.

Hematologic Toxicity: Treatment with Gleevec is associated with anemia, neutropenia and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month and periodically thereafter as clinically indicated (for example every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML.

Severe Congestive Heart Failure and Left Ventricular Dysfunction: Severe congestive heart failure and left ventricular dysfunction have occasionally been reported in patients taking GLEEVEC. Most of the patients with reported cardiac events have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking GLEEVEC compared to 0.3% of patients taking IFN + Ara-C. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated.

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with GLEEVEC. Liver function tests (transaminases, bilirubin and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with GLEEVEC.

Hemorrhage: In the newly diagnosed CML trial, 1.5% of patients had Grade 3/4 hemorrhage.

Gastrointestinal Disorders: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of GLEEVEC.

Toxicities From Long-Term Use: It is important to consider potential toxicities suggested by animal studies, specifically, liver, kidney and cardiac toxicity and immunosuppression.

Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mesangial expansion and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these monkeys. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans). Additional long-term toxicities were identified in a 2-year rat study. Histopathological examination of the treated rats that died on study revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Non-neoplastic lesions seen in this 2-year study that were not identified in earlier preclinical studies were of the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

DRUG INTERACTIONS

Agents Inducing CYP3A Metabolism
Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of GLEEVEC, increased GLEEVEC oral-dose clearance by 3.8-fold, which significantly (p<0.05) decreased mean Cmax and AUC. If alternative treatment cannot be administered, a dose adjustment should be considered.

Agents Inhibiting CYP3A Metabolism
There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when GLEEVEC was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). Caution is recommended when administering GLEEVEC with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, alazanavir, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole).

Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isozyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.

Interactions with Drugs Metabolized by CYP3A4
GLEEVEC increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- to 3.8-fold, respectively, following an inhibition of the CYP3A4 by GLEEVEC. Particular caution is recommended when administering GLEEVEC with CYP3A4 substrates that have a narrow therapeutic window (e.g., alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, piomozide, quinidine, sirolimus or tacrolimus).

Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazole-benzodiazepines, dihydropyrimidine calcium channel blockers, statins, HMG-CoA reductase inhibitors, etc.). Because warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low molecular weight or standard heparin instead of warfarin.

Interactions with Drugs Metabolized by CYP2D6
In vitro, Gleevec inhibits the cytochrome P450 isozyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when co-administered with Gleevec. No specific studies have been performed and caution is recommended.

Interaction with Acetaminophen
In vitro, GLEEVEC inhibits acetaminophen O-glucuronidation (K, value of 58.5 µM) at therapeutic levels. Systemic exposure to acetaminophen is expected to be increased when co-administered with Gleevec. No specific studies in humans have been performed and caution is recommended.

NONCLINICAL TOXICITY

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year rat carcinogenesis study administration of imatinib at 15, 30 and 60 mg/kg/day resulted in a statistically significant reduction in the longevity of males at 60 mg/kg/day and females at ≤30 mg/kg/day. Target organs for non-plastic changes were the kidneys (renal tubule and renal pelvis), urinary bladder, urethra, prepuce and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. Neoplastic lesions were not seen at 30 mg/kg/day for the kidneys, urinary bladder, urethra, small intestine, parathyroid glands, adrenal glands and non-glandular stomach and 15 mg/kg/day
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for the preputial and clitoral gland. The papilloma/carcinoma of the preputial/clitoral gland were noted at 30 and 60 mg/kg/day, representing approximately 0.5 to 4 or 0.3 to 2.4 times the human daily exposure (based on AUC) at 400 mg/day or 800 mg/day, respectively, and 0.4 to 3.0 times the daily exposure in children (based on AUC) at 340 mg/m²/day. The renal tubule adenoma/carcinoma, renal pelvis transitional cell neoplasms, the urinary bladder and urethra transitional cell papillomas, the small intestine adenocarcinomas, the parathyroid glands adenomas, the benign and malignant medullary tumours of the adrenal glands and the non-glandular stomach papillomas/carcinomas were noted at 60 mg/kg/day. The relevance of these findings in the rat carcinogenicity study for humans is not known.

Positive genotoxic effects were obtained for imatinib in an in vitro mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an in vitro bacterial cell assay (Ames test), an in vitro mammalian cell assay (mouse lymphoma) and an in vitro rat micronucleus assay.

In a study of fertility, male rats were dosed for 70 days prior to mating and female rats were dosed 14 days prior to mating and through to gestational Day 6. Testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourth the maximum clinical dose of 800 mg/day based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). The fertility of male and female rats was not affected.

In a pre- and postnatal development study in female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) from gestational Day 6 until the end of lactation, red vaginal discharge was noted on either gestational Day 14 or 15. In the first generation offspring, the offspring at this dose level, mean body weights were reduced from birth until weaning. First generation offspring fertility was not affected but reproductive effects were noted at 45 mg/kg/day, including an increased number of resorptions and a decreased number of viable fetuses.

Fertility was not affected in the preclinical fertility and early embryonic development study, although lower tests and epididymal weights as well as a reduced number of motile sperm were observed in the high dose male rats. In the preclinical pre- and postnatal study in rats, fertility in the first generation offspring was also not affected by GLEEVEC.

Human studies on male patients receiving GLEEVEC and its effect on male fertility and spermatogenesis have not been performed. Male patients concerned about their fertility on GLEEVEC treatment should consult their physician.

PATIENT COUNSELING INFORMATION

Dosage and Administration

Patients should be informed to take GLEEVEC exactly as prescribed, not to change their dose or to stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose. Patients should be advised to take GLEEVEC with a meal and a large glass of water.

Pregnancy and Breast-Feeding

Patients should be advised to inform their doctor if they are or think they may be pregnant. Patients should also be advised not to breast-feed while taking GLEEVEC.

Adverse Reactions

Patients should be advised to tell their doctor if they experience side effects during GLEEVEC therapy, including fever, shortness of breath, blood in their stool, jaundice, sudden weight gain, symptoms of cardiac failure, or if they have a history of cardiac disease or risk factors for cardiac failure.

Drug Interactions

Patients should be advised not to take any other medications, including over-the-counter medications, such as acetaminophen or herbal products, without talking to their doctor or pharmacist first. Examples of other medications that should not be taken with GLEEVEC are warfarin, erythromycin and phenylbutazone. Patients should also be advised to tell their doctor if they are taking or plan to take iron supplements. Patients should also avoid grapefruit juice and other foods known to inhibit CYP3A4 while taking GLEEVEC.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category D (See WARNINGS AND PRECAUTIONS)

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% of the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from GLEEVEC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of GLEEVEC was similar in older and younger patients.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of both imatinib and its major metabolite, CGP74588, was assessed in 64 cancer patients with varying degrees of hepatic impairment (Table 1) at imatinib doses ranging from 100-800 mg. Exposure to both imatinib and CGP74588 was comparable between each of the mildly and moderately hepatically-impaired groups and the normal group. Patients with severe hepatic impairment tend to have higher exposure to both imatinib and its metabolite than patients with normal hepatic function. At steady state, the mean Cmax/dose and AUC/dose for imatinib increased by about 63% and 45%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function. The mean Cmax/dose and AUC/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function.

Table 1: Liver Function Classification

<table>
<thead>
<tr>
<th>Liver Function Test</th>
<th>Normal (n=14)</th>
<th>Mild (n=30)</th>
<th>Moderate (n=20)</th>
<th>Severe (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td>≤ULN</td>
<td>&gt;1.0-1.5xULN</td>
<td>&gt;1.5-5xULN</td>
<td>&gt;5xULN</td>
</tr>
<tr>
<td>SGOT</td>
<td>≤ULN</td>
<td>&gt;ULN (can be normal if Total Bilirubin is ≤ULN)</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

ULN=upper limit of normal for the institution

Renal Impairment

No clinical studies were conducted with GLEEVEC in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice. The majority of GLEEVEC-treated CML patients experienced adverse reactions at some time (see Table 2). Most reactions were of mild-to-moderate grade, but drug was discontinued for drug-related adverse reactions in 2.4% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon-alpha therapy, 4% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse reactions were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash. Edema was most frequently petechial or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of GLEEVEC. The frequency of severe superficial edema was 1.5%-6%.

A variety of adverse reactions represent local or general fluid retention, including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These reactions appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day) and are more common in the elderly. These reactions were usually managed by interrupting GLEEVEC treatment and with diuretics or other appropriate supportive care measures. A few of these reactions may
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be serious or life threatening and one patient with blast crisis died with pleural effusion, congestive heart failure and renal failure.

Table 2

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Grades</th>
<th>CTC Grades 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Retention</td>
<td>61.7</td>
<td>11.1</td>
</tr>
<tr>
<td>-Supraventricular</td>
<td>59.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Other Fluid Retention Reactions①</td>
<td>6.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>49.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>49.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>47.0</td>
<td>44.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4</td>
<td>43.3</td>
</tr>
<tr>
<td>Rash and Related Terms</td>
<td>40.1</td>
<td>26.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.8</td>
<td>67.0</td>
</tr>
<tr>
<td>Headache</td>
<td>37.0</td>
<td>43.3</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>31.4</td>
<td>38.1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>36.5</td>
<td>25.9</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>28.9</td>
<td>21.2</td>
</tr>
<tr>
<td>-GI Hemorrhage</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>-CNS Hemorrhage</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>24.1</td>
<td>38.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22.5</td>
<td>27.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18.9</td>
<td>8.3</td>
</tr>
<tr>
<td>Cough</td>
<td>20.0</td>
<td>23.1</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>18.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>21.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17.8</td>
<td>42.6</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>15.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.7</td>
<td>18.6</td>
</tr>
<tr>
<td>Depression</td>
<td>14.9</td>
<td>35.8</td>
</tr>
<tr>
<td>Influenza</td>
<td>13.8</td>
<td>6.2</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>11.3</td>
<td>15.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>11.4</td>
<td>14.4</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11.4</td>
<td>6.0</td>
</tr>
</tbody>
</table>

① All adverse reactions occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

② Other fluid retention reactions include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated and fluid retention not otherwise specified.

Hematologic Toxicity

Cytopenias, particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥750 mg (Phase 1 study). However, the occurrence of cytopenias in CML patients was also dependent on the stage of the disease. In patients with newly diagnosed CML (see Table 3), cytopenias were less frequent than in the other CML patients. The frequency of grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase. The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks and from 2 to 4 weeks, respectively. These reactions can usually be managed with either a reduction of the dose or an interruption of treatment with GLEEVEC, but in rare cases require permanent discontinuation of treatment.

Table 3

<table>
<thead>
<tr>
<th>CTC Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLEEVEC® N=551</td>
<td>6.1</td>
<td>3.1</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>IFN=ara-C N=553</td>
<td>3.3</td>
<td>0.5</td>
<td>1.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Hematology Parameters

-Neutropenia* | 13.1 | 3.6 | 20.8 | 4.5 |
-Thrombocytopenia* | 8.5 | 0.4 | 15.9 | 0.6 |
-Anemia | 3.3 | 1.1 | 4.1 | 0.2 |

Biochemistry Parameters

-Elevated Creatinine | 0 | 0 | 0.4 | 0 |
-Elevated Bilirubin | 0.9 | 0.2 | 0.2 | 0 |
-Elevated Alkaline Phosphatase | 0.2 | 0 | 0.8 | 0 |
-Elevated SGOT/SGPT | 4.7 | 0.5 | 7.1 | 0.4 |

*P<0.0001 (difference in Grade 3 plus 4 abnormalities between the two treatment groups)

Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in approximately 5% of CML patients and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately 1 week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1.0% of CML patients. One patient, who was taking acetylsalicylic acid regularly for fever, died of acute liver failure.

Adverse Reactions in Other Subpopulations

In older patients (≥65 years old), with the exception of edema, which was more frequent, there was no evidence of an increase in the incidence or severity of adverse reactions. In women there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema, headache, nausea, rigor, vomiting, rash and fatigue. No differences were seen related to race but the subsets were too small for proper evaluation.

Additional Data From Multiple Clinical Trials

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse reactions have been reported during clinical trials of GLEEVEC. These reactions are included based on clinical relevance.

Cardiovascular: Infrequent: cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness; Rare: periarteritis

Clinical Laboratory Tests: Infrequent: blood CK, LDH increased

Dermatologic: Less common: dry skin, alopecia; Infrequent: exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura, psoriasis; Rare: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome)

Gastrointestinal: Less common: abdominal distension, gastroesophageal reflux, mouth ulceration; Infrequent: gastric ulcer, gastroenteritis, gastritis; Rare: colitis, jejunal obstruction, pancreatitis, diverticulitis, tumor hemorrhage/tumor necrosis, gastrointestinal perforation

General Disorders and Administration Site Conditions: Rare: tumor necrosis

Hematologic: Infrequent: pancytopenia; Rare: aplastic anemia

Hepatobiliary: Uncommon: hepatitis; Rare: hepatic failure

Hypersensitivity: Rare: angioedema

Infections: Infrequent: sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: Infrequent: hypophosphatemia, dehydration, gout, thyroid dysfunction; Rare: hyperkalemia, hyponatremia

Musculoskeletal: Less common: joint swelling; Infrequent: sciatica, joint and muscle stiffness; Rare: avascular necrosis/hip osteonecrosis

Nervous System/Psychiatric: Less common: paresthesia; Infrequent: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment; Rare: increased intracranial pressure, cerebral edema (including fatalities), confusion, convulsions

Renal: Infrequent: renal failure, urinary frequency, hematuria
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**Reproductive:** Infrequent: breast enlargement, menorrhagia, sexual dysfunction

**Respiratory:** Rare: interstitial pneumonitis, pulmonary fibrosis

**Special Senses:** Less common: conjunctivitis, vision blurred; Infrequent: conjunctival hemorrhage, dry eye, vertigo, tinnitus; Rare: macular edema, papilledema, retinal hemorrhage, glaucoma, vitreous hemorrhage

**Vascular Disorders:** Rare: thrombosis/embolism

**Postmarketing Experience**

The following additional adverse reactions have been identified during post-approval use of GLEEVEC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In some cases of bullosal dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, reported during postmarketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign postmarketing reports have described cases in which patients tolerated the reintroduction of GLEEVEC therapy after resolution or improvement of the bullous reaction. In these instances, GLEEVEC was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

There have been post-marketing reports, including fatalities, of cardiac tamponade, cerebral edema, increased intracranial pressure and papilledema in patients treated with GLEEVEC.

**OVERDOSE**

Experience with doses greater than 800 mg is limited. Isolated cases of GLEEVEC overdose have been reported. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of GLEEVEC daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse reactions. Another patient developed severe muscle cramps after taking 1,600 mg of GLEEVEC daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient, who was prescribed 400 mg daily, took 800 mg of GLEEVEC on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse reactions occurred and the patient resumed therapy.

**DOSAGE AND ADMINISTRATION**

Therapy should be initiated by a physician experienced in the treatment of patients with hematological malignancies or malignant sarcomas, as appropriate. The prescribed dose should be administered orally, with a meal and a large glass of water. Joses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100 mg tablet and 200 mL for a 400 mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

For daily dosing of 800 mg and above, dosing should be accomplished using the 400 mg tablet to reduce exposure to iron.

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

The recommended dose of GLEEVEC is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopeina in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6–12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

**Dose Modification Guidelines**

Concomitant Strong CYP3A4 Inducers: The use of concomitant strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampacin, phenobarbital). If patients must be co-administered a strong CYP3A4 Inducer, based on pharmacokinetic studies, the dosage of GLEEVEC should be increased by at least 50% and clinical response should be carefully monitored. [See DRUG INTERACTIONS.]

**Hepatic Impairment:** Patients with mild and moderate hepatic impairment do not require a dose adjustment and should be treated per the recommended dose. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment.

**Dose Adjustment for Hepatotoxicity and Non-Hematologic Adverse Reactions**

If elevations in bilirubin >3x the institutional upper limit of normal (IULN) or in liver transaminases >5x IULN occur, GLEEVEC should be withheld until bilirubin levels have returned to <1.5x IULN and transaminase levels to <2.5x IULN. In adults, treatment with GLEEVEC may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg, 600 mg to 400 mg or 800 mg to 600 mg). In children, daily doses can be reduced under the same circumstances from 340 mg/m²/day to 260 mg/m²/day or from 260 mg/m²/day to 200 mg/m²/day, respectively.

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), GLEEVEC should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

**Dose Adjustment for Hematologic Adverse Reactions**

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 4.

| Chronic Phase CML (starting dose 400 mg) | ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L | 1. Stop GLEEVEC until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L |
| Ph+ CML: Accelerated Phase and Blast Crisis (starting dose 600 mg) | ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L | 2. Resume treatment with GLEEVEC at the original starting dose of 400 mg or 600 mg |

1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)

2. If cytopenia is unrelated to leukemia, reduce dose of GLEEVEC to 400 mg

3. If cytopenia persists 2 weeks, reduce further to 300 mg

4. If cytopenia persists 4 weeks and is still unrelated to leukemia, stop GLEEVEC until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L and then resume treatment at 300 mg

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Response with toleration!

Please see brief prescribing information and references on following pages.
IMPORTANT SAFETY INFORMATION: Venofer® (iron sucrose injection, USP) is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofer® or any of its inactive components, and in patients with anemia not caused by iron deficiency. Hypersensitivity reactions have been reported with IV iron products. Hypotension has been reported frequently in non-dialysis-dependent-chronic kidney disease (CKD) patients receiving IV iron. Hypotension following administration of Venofer® may be related to rate of administration and total dose delivered. In a multi-dose efficacy study in non-dialysis dependent-CKD patients (N=91), the most frequent adverse events (≥5%) whether or not related to Venofer® administration, were taste disturbance, peripheral edema, diarrhea, constipation, nausea, dizziness, and hypertension.

The only first-line IV iron for pre-dialysis CKD patients...

In treatment of iron deficiency anemia
- Raises hemoglobin levels and improves iron stores
- Effective with or without erythropoietin

With a demonstrated safety profile
- No test dose required, no black box warning
- Contains no dextran or modified dextran
- Greater tolerability than oral iron with fewer gastrointestinal symptoms

*100 mg vials and ampules worldwide from 1993 to 2007.

Venofer®
iron sucrose injection, USP
Reinvigorating anemia management.

*Over 7 million patients treated with 143 million units*
**Venofer**

Iron sucrose injection, USP

**Therapeutic Class:** Hematinic

**Brief Summary** (See Package Insert For Full Prescribing Information)

**Precautions:**

- Venofer® should be administered with caution in patients with evidence of iron overload, as patients with known hypersensitivity to Venofer® or any of its inactive components.
- The use of Venofer® is contraindicated in patients with evidence of iron overload.

**Contraindications:**

- Venofer® was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, and in the mouse micronucleus test.

**Pregnancy Category B:**

- Venofer® has been reported frequently in hemoglobin-dependent clinical trials with evidence of iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines. Particular caution should be exercised to avoid iron overload.

**Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients**

Table 2. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients with NDD-CKD by Dose Group (Multisite Safety Population)

<table>
<thead>
<tr>
<th>Adverse Events</th>
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<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venofer®</td>
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<td>0</td>
</tr>
<tr>
<td>Oral iron</td>
<td>3.3</td>
<td>3.3</td>
</tr>
</tbody>
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**Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients**

Table 3. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients with NDD-CKD by Dose Group (Multisite Safety Population)

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</table>

**Preclinical Data:**

- Venofer® was administered in a total cumulative dose of 1,000 mg over a 14 day period as a 200 mg IV dose daily, and no toxic effects were observed.

**Dosage and Administration:**

- The dosage of Venofer® is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron.

**References:**

Chemoimmunotherapy for DLBCL. In Studies 6 and 7, the following adverse reactions, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: pancytopenia (95% vs. 46%), lung toxicity (35% vs. 24%), cardiac disorders (23% vs. 15%), and infections (21% vs. 18%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions. In Study 7, a review of patient records was conducted to determine whether any adverse reactions associated with the R-CHOP regimen reported in the study occurred more frequently among patients in the R-CHOP arm than those in the CHOP arm. Due to the small number of cases and the lack of adequate controls, this analysis was not done for any specific adverse reactions. The results of the analysis indicate that the incidence of adverse reactions observed in patients receiving the R-CHOP regimen in Study 7 was no greater than that observed in patients receiving CHOP alone. The most common adverse reactions reported in combination with rituximab in the clinical trials were infections, neutropenia, anemia, and nausea. Infections were generally mild to moderate and occurred most frequently during the first two cycles of treatment. Neutropenia was generally mild to moderate and occurred in approximately 20% of patients. Anemia was generally mild to moderate and occurred in approximately 30% of patients. Nausea was generally mild to moderate and occurred in approximately 30% of patients.

In studies of patients with low-grade, follicular, or DLBCL NHL, rituximab was generally well tolerated, and the most frequently observed adverse reactions were infusion reactions, febrile infections, infections, neutropenia, and asthenia. The overall incidence of infections was 45% (bacterial 22%, viral 23%, fungal 1%, and other 1%). Neutropenia was observed in 22% of patients, and asthenia was observed in 36% of patients. The incidence of infusion reactions was highest during the first infusion (7%) and decreased with each subsequent infusion. In studies of patients with lymphoma, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 35% (bacterial 21%, viral 10%, fungal 1%, and other 1%). Neutropenia was observed in 23% of patients, and asthenia was observed in 35% of patients. The incidence of infusion reactions was highest during the first infusion (11%) and decreased with each subsequent infusion. In studies of patients with high-grade NHL, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 29% (bacterial 19%, viral 10%, fungal 1%, and other 1%). Neutropenia was observed in 30% of patients, and asthenia was observed in 45% of patients. The incidence of infusion reactions was highest during the first infusion (11%) and decreased with each subsequent infusion. In studies of patients with high-grade NHL, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 35% (bacterial 21%, viral 10%, fungal 1%, and other 1%). Neutropenia was observed in 23% of patients, and asthenia was observed in 35% of patients. The incidence of infusion reactions was highest during the first infusion (7%) and decreased with each subsequent infusion. In studies of patients with non-Hodgkin’s lymphoma, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 34% (bacterial 20%, viral 10%, fungal 1%, and other 1%). Neutropenia was observed in 27% of patients, and asthenia was observed in 43% of patients. The incidence of infusion reactions was highest during the first infusion (7%) and decreased with each subsequent infusion. In studies of patients with high-grade NHL, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 41% (bacterial 20%, viral 20%, fungal 1%, and other 1%). Neutropenia was observed in 31% of patients, and asthenia was observed in 49% of patients. The incidence of infusion reactions was highest during the first infusion (7%) and decreased with each subsequent infusion. In studies of patients with high-grade NHL, the most frequently observed adverse reactions were infusion reactions, fever, chills, and asthenia. The overall incidence of infusion reactions was 8% (7% during cycle 2, 3%, and 1%), and the incidence of fever, chills, and asthenia was 9%, 7%, and 7%, respectively. The overall incidence of infections was 35% (bacterial 21%, viral 10%, fungal 1%, and other 1%). Neutropenia was observed in 23% of patients, and asthenia was observed in 35% of patients. The incidence of infusion reactions was highest during the first infusion (11%) and decreased with each subsequent infusion.
Free Blood Content Alerts and How to Use Them

What are content alerts? Blood content alerts are e-mails sent to you notifying you that new content has been published on Blood Online. You can ask to be alerted about new issues (eTOC alerts), about future article lists (fTOC alerts), about new articles in a particular online collection (collection alerts), about prepublication of manuscripts on First Edition Papers, or about customized bibliographic searches (CiteTrack alerts).

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When planning a treatment course for DLBCL

Take the essential path toward improved survival

RITUXAN+CHOP is proven to prolong survival in DLBCL

- At 7 years, 8 cycles of RITUXAN+CHOP increased overall survival (OS) from 36% to 53% compared with CHOP alone.
- At 5 years, 8 cycles of RITUXAN+CHOP increased OS from 46% to 58% compared with CHOP alone.

**Boxed WARNINGs and Additional Important Safety Information**

The most important serious adverse reactions of RITUXAN are fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation. The most common adverse reactions of RITUXAN (incidence ≥25%) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.

RITUXAN in Combination with CHOP Chemotherapy for DLBCL: The following adverse reactions, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: pyrexia (55% vs 40%), lung disorder (31% vs 24%), cardiac disorder (25% vs 21%), and chills (13% vs 4%). In the GELA LNH 98-5 study, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs 7%) and lung disorder (6% vs 3%). Other Grade 3 or 4 adverse reactions reported more frequently among patients receiving R-CHOP were viral infection (GELA LNH 98-5 study), neutropenia (GELA LNH 98-5 and MinT studies), and anemia (MinT study).

Please see brief summary of prescribing information on adjacent page.

Attention Healthcare Provider: Provide Medication Guide to patient prior to RITUXAN infusion.

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Mentor (mĕn´tôr´) n.
A wise and trusted counselor or teacher*

Honor your mentor for being a wise and trusted counselor and so much more by nominating him or her for the ASH Mentor Award. This is a wonderful way to say thank you to a mentor who influenced your career.

The American Society of Hematology (ASH) grants two Mentor Awards each year at the annual meeting—one in basic science and one in clinical investigation.

The nomination deadline is May 4, 2009.

For more information, please visit the ASH Web site, www.hematology.org/education/awards/mentorship.cfm
How Would You Like To Receive €75,000 to Conduct Research in Another Country?

The EHA-ASH® Research Exchange Award Can Make This Possible.
The American Society of Hematology (ASH) and the European Hematology Association (EHA) have partnered to create the EHA-ASH Research Exchange Award to allow hematologists to gain a cross-cultural educational experience by conducting research in another country for up to two years.

This award is intended to allow awardees from the United States, Canada, or Mexico to complete a research project in Europe and awardees from Europe to complete a research project in North America.

This award is open to ASH or EHA members who have a doctoral degree and are in a post-graduate hematology training program or actively engaged in laboratory or clinical research.

Each award recipient will receive 75,000 euro to cover:

- Supplies
- Travel expenses
- Housing
- A per diem

In addition, travel stipends to attend the ASH annual meeting or EHA congress will be offered during the award period.

The deadline to submit a letter-of-intent to ASH is May 15, 2009. Visit the ASH Web site for complete award details and instructions on how to apply. All letters of intent must be submitted in English.

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QUESTIONS? If you have any questions or need additional information, please contact the ASH Awards Manager at +1 202-776-0544 or development@hematology.org.
Nplate™ (romiplostim)

Brief Summary

WARNINGS AND PRECAUTIONS

Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

Nplate™ administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. In clinical studies, reticulin formation was observed in four of 271 patients because of bone marrow reticulin deposition. Six additional patients had reticulin observed upon bone marrow biopsy. All 10 reported cases of reticulin deposition were observed. Nplate™ doses ≥ 5 mcg/kg and six received doses ≥ 10 mcg/kg. Progression to marrow fibrosis with cytopenias was not reported in the pharmacology studies. In the extension study, one patient with ITP and hemopoietic anemia developed narrow fibrosis with collagen during Nplate™ therapy. Clinical studies have not excluded a risk for marrow cytopenias. Prior to initial Nplate™, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable Nplate™ dose, examine peripheral blood smears for evidence of narrow fibrosis or worsening morphologic (eg, teardrop and nucleated red blood cells, immature white blood cells) or cytopenias(s). If the patient develops new or worsening morphologic abnormalities or cytopenias(s), discontinue treatment with Nplate™ and consider a bone marrow biopsy, including staining for fibrin [see Adverse Reactions (6.1)].

Worsened Thrombocytopoiesis After Cessation of Nplate™

Discontinuation of Nplate™ may result in thrombocytopoiesis of greater severity than was present prior to Nplate™ therapy. This worsening thrombocytopoiesis may increase the patient's risk of bleeding, particularly if Nplate™ is discontinued while the patient is on anticoagulants or platelet agents. In clinical studies of patients with chronic ITP who had Nplate™ discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate™ therapy. This worsened thrombocytopoiesis resolved within 14 days. Following discontinuation of Nplate™, observe CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation. Use alternative treatments for worsening thrombocytopoiesis, according to current treatment guidelines [see Adverse Reactions (6.1)].

Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of Nplate™ or medication errors that result in excessive Nplate™ doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was similar between Nplate™ and placebo. To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate™ in an attempt to achieve and maintain a platelet count of ≥ 300 x 10^9/L [see Dosage and Administration (2.2)].

Lack or Loss of Response to Nplate™

If Nplate™ may be a consideration if the patient develops thrombocytopenia of greater severity than was present prior to Nplate™ therapy. The maximum Nplate™ dose may be reached due to ongoing reticulin deposition during the extension study, one patient with ITP and hemopoietic anemia developed narrow fibrosis with collagen during Nplate™ therapy. Clinical studies have not excluded a risk for marrow cytopenias. The incidence of hematologic malignancy was low and similar between Nplate™ and placebo. It is not known whether Nplate™ is excreted in human milk; however, human IgG is excreted in human milk. Published data suggest that breast milk and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Nplate™, a decision should be made whether to discontinue nursing or to discontinue Nplate™, taking into account the importance of Nplate™ to the mother and the known benefits of nursing.

Pediatric Use

The safety and effectiveness in pediatric patients (<18 years) have not been established.

Geriatric Use

Of the 271 patients who received Nplate™ in ITT clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in clinical trials. The incidence of adverse drug reactions was not increased in patients ≥ 65 years of age. The incidence of adverse drug reactions was not increased in patients ≥ 75 years of age. The incidence of adverse drug reactions was not increased in patients ≥ 85 years of age. The incidence of adverse drug reactions was not increased in patients ≥ 95 years of age. The incidence of adverse drug reactions was not increased in patients ≥ 105 years of age.

OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In this case, discontinue Nplate™ and monitor platelet counts. Reinitiate treatment with Nplate™ in accordance with dosing and administration recommendations [see Dosage and Administration (2.2)].

Rx Only. This brief summary is based on Nplate™ prescribing information v1

Manufactured by:
Amgen Inc.
One Amgen Center Drive
 Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more U.S. Patents, including U.S. Patent Nos. 8,635,809 and 7,189,827, as well as other patents or patents pending.

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References:

Increased platelet production.  
Sustained platelet response.  
Reduced concurrent medication exposure.

Patient results may vary.

Nplate™ is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Nplate™ should not be used in an attempt to normalize platelet counts.

IMPORTANT SAFETY INFORMATION
Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation. Additional risks include Bone Marrow Fibrosis, Thrombotic/Thromboembolic Complications, Lack or Loss of Response to Nplate™, Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS).
Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

Monitor CBC’s, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of Nplate™ therapy.

Nplate™ is available only through a restricted distribution program called Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate™ and Patients) Program.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

Please see Brief Summary of Prescribing Information on adjacent page.