Immune reconstitution after allogeneic transplantation: an update (p 3861)

Impact of cholesterol on hematopoietic progenitor mobilization (p 3886)

c-Kit and IL-33 signaling in mast cells (p 3899)

Cooperating tumor suppressors in 13q14-deleted CLL (p 3916)

Regulation of red cell alloantibody responses via exposure to microbial epitopes (p 3989)

Cover: Platelets help control specification of blood versus lymphatic vessels (p 3997)

www.bloodjournal.org
WARNING: QT PROLONGATION AND SUDDEN DEATHS
TASIGNA prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

ADVERSE REACTIONS: Treatment with TASIGNA can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. In CML-CP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, and vomiting.

TASIGNA (nilotinib) capsules is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of TASIGNA is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Please see Important Safety Information, including Boxed WARNING, and brief summary of Prescribing Information on following pages.
TASIGNA delivers cytogenetic response in the chronic phase after Gleevec

- 40% of patients achieved an unconfirmed major cytogenetic response (MCyR) [95% CI: 33-46] \(^1\)
- 28% of patients achieved an unconfirmed complete cytogenetic response (CCyR) [95% CI: 22-34] \(^1\)
- 12% of patients achieved an unconfirmed partial cytogenetic response (PCyR) [95% CI: 8-16] \(^1\)
- Rapid responses: 2.8 months median time to MCyR \(^1\)

Important study design information \(^1\)

- A single, open-label, multicenter study was conducted to evaluate efficacy and safety in patients with Ph+ CML in the chronic phase with resistance or intolerance to Gleevec. At the time of data cutoff, 280 patients with a minimum follow-up of 6 months were enrolled.
- Of the 280 patients, 232 were evaluable for efficacy. The efficacy end point was unconfirmed MCyR, which included CCyR and PCyR.
- CyR criteria: CCyR [≥90% Ph+ metaphases] or PCyR [1%-35%]. Cytogenetic responses were based on the percentage of Ph+ metaphases among ≥20 metaphase cells in each bone marrow sample.

Prescribe TASIGNA for your patients in the chronic phase who are no longer responding or are intolerant to Gleevec

- Patients who are not meeting minimum treatment goals:
  - Complete hematologic response (CHR) at 3 months, CyR at 6 months, or MCyR at 12 months
- Patients who lose HR or CyR at any time
- Patients who cannot tolerate Gleevec

TASIGNA® (NILOTINIB) CAPSULES - IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

TASIGNA (nilotinib) is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of TASIGNA is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

WARNING: QT PROLONGATION AND SUDDEN DEATHS

TASIGNA prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

WARNINGS AND PRECAUTIONS

Myelosuppression

Treatment with TASIGNA can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding TASIGNA temporarily or dose reduction.

QT Prolongation

TASIGNA prolongs the QT interval. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated, and following dose adjustments. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically.

Significant prolongation of the QT interval may occur when TASIGNA is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided. The presence of hypokalemia and hypomagnesemia may further enhance this effect.

Sudden Deaths

There were sudden deaths reported in the safety population and in the expanded access program. Ventricular repolarization abnormalities may have contributed to their occurrence.

Elevated Serum Lipase

Caution is recommended in patients with a history of pancreatitis. Check serum lipase levels monthly or as clinically indicated.

Hepatotoxicity

Serum bilirubin and hepatic transaminases

The use of TASIGNA may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Hepatic function tests should be checked monthly or as clinically indicated.

Electrolyte Abnormalities

TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating TASIGNA and monitor periodically during therapy.

Hepatic Impairment

Nilotinib exposure is increased in patients with impaired hepatic function. A lower starting dose is recommended for patients with mild to severe hepatic impairment and QT interval should be monitored closely.

Drug Interactions

The concomitant use of QT prolonging drugs and strong inhibitors or inducers of CYP3A4 should be avoided as they may affect serum concentration of TASIGNA.

Concomitant strong CYP3A4 inhibitors

The concomitant use of strong CYP3A4 inhibitors or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, and pimozide) should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with TASIGNA be interrupted. If interruption of treatment with TASIGNA is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval, and a dose reduction to ½ the daily dose is recommended (400 mg once daily). If the strong inhibitor is discontinued, a washout period should be allowed before TASIGNA is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors. Grapefruit products and other foods that are known to inhibit CYP3A4 should also be avoided.

Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be
avoided (including, but not limited to, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Patients should also refrain from taking St John’s Wort. If patients must be co-administered a strong CYP3A4 inducer, the dose of TASIGNA may need to be increased, depending on patient tolerability. If the strong inducer is discontinued, the TASIGNA dose should be reduced to the indicated TASIGNA dose. TASIGNA is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6, and UGT1A1. In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8, and CYP2C9, and decrease the concentrations of drugs which are eliminated by these enzymes. Single-dose administration of TASIGNA to healthy subjects did not change the pharmacokinetics and pharmacodynamics of warfarin (a CYP2C9 substrate). The ability of TASIGNA to induce metabolism has not been determined in vivo. Caution should be exercised when co-administering TASIGNA with substrates for these enzymes that have a narrow therapeutic index. TASIGNA inhibits human P-glycoprotein. If TASIGNA is administered with drugs that are substrates of Pgp, increased concentrations of the substrate are likely and caution should be exercised.

Food Effects
Food increases blood levels of TASIGNA. Patients should avoid food 2 hours before and at 1 hour after the dose is taken.

Lactose
Since the capsules contain lactose, TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or of glucose-galactose malabsorption.

Use in Pregnancy
There are no adequate and well controlled studies of TASIGNA in pregnant women. However, TASIGNA may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should avoid becoming pregnant while taking TASIGNA and should be advised of the potential hazard to the fetus if they do.

ADVERSE REACTIONS
In chronic phase patients, the most commonly reported adverse reactions (>10%) were rash (33%), pruritus (29%), nausea (31%), fatigue (28%), headache (31%), constipation (21%), diarrhea (22%), and vomiting (21%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (28%), neutropenia (28%), elevated lipase (15%), and hyperglycemia (11%). In accelerated phase patients, the most commonly reported adverse reactions (>10%) were rash (28%), pruritus (20%), and constipation (18%). The most common (>10%) Grade 3/4 adverse reactions were thrombocytopenia (37%), neutropenia (37%), anemia (23%), and elevated lipase (17%). Other serious adverse reactions included pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, and pyrexia (Grade 3/4: 2%).

DOSE ADJUSTMENTS OR MODIFICATIONS
TASIGNA may need to be temporarily withheld and/or dose reduced for QT prolongation, hematological toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors. With concomitant use of strong CYP3A4 inducers, the dose of TASIGNA may need to be increased, depending on patient tolerability.

For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. For Grade 3 to 4 bilirubin elevations, dosing should be withheld, and may be resumed at 400 mg once daily.

Hepatic impairment
If possible, consider alternative therapies. If TASIGNA must be administered to patients with hepatic impairment, a lower starting dose is recommended in patients with hepatic impairment and QT interval should be monitored. The following dose reduction should be considered:
For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 400 mg in the morning and 200 mg in the evening (12 hours apart) per day followed by dose escalation to 400 mg twice daily based on patient tolerability should be considered. For patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 200 mg twice daily followed by a sequential dose escalation to 400 mg in the morning and 200 mg in the evening (12 hours apart) per day and then to 400 mg twice daily based on patient tolerability should be considered.

OTHER PATIENTS IN WHOM TASIGNA SHOULD BE USED WITH CAUTION
TASIGNA should not be used during pregnancy. Sexually active female patients should use effective contraception during treatment. Women should not breast feed while taking TASIGNA. The safety and effectiveness of TASIGNA in pediatric patients have not been established.
Table 3. Dose Adjustments for Selected Non-hematologic Laboratory Abnormalities

| Table 3. Dose Adjustments for Selected Non-hematologic Laboratory Abnormalities |
|-----------------|-----------------|-----------------|
| Elevated serum lipase or amylase ≥Grade 3 | 1. Withhold Tasigna, and monitor serum lipase or amylase 2. Resume treatment at 400 mg once daily if serum lipase or amylase return to <Grade 1 |
| Elevated bilirubin ≥Grade 3 | 1. Withhold Tasigna, and monitor bilirubin 2. Resume treatment at 400 mg once daily if bilirubin return to <Grade 1 |
| Elevated hepatic transaminases ≥Grade 3 | 1. Withhold Tasigna, and monitor hepatic transaminases 2. Resume treatment at 400 mg once daily if hepatic transaminases return to <Grade 1 |

Other Non-hematologic Toxicities: If other clinically significant moderate or severe non-hematologic toxicity develops, dosing should be withheld, and may be resumed at 400 mg once daily when the toxicity has resolved. If clinically appropriate, escalation of the dose back to 400 mg twice daily should be considered. For Grade 3 or 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Serum lipase levels should be tested monthly or as clinically indicated. For Grade 3 to 4 bilirubin elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated. [See Warnings and Precautions (5) and Use in Specific Populations (8) in the full prescribing information].

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, alranazine, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit products may also increase serum concentrations of nilotinib and should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, 400 mg once daily (a dose reduction to 1/2 of the original daily dose) is predicted to adjust the nilotinib AUC to the AUC observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the Tasigna dose is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors. [See Boxed Warning, Warnings and Precautions (5.2 and 5.7) and Drug Interactions (7.2) in the full prescribing information].

Concomitant Strong CYP3A4 Inducers: The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Patients should also refrain from taking St. John’s Wort. If patients must be co-administered a strong CYP3A4 inducer, the dose of Tasigna may need to be increased, depending on patient tolerability. If the strong inducer is discontinued the nilotinib dose should be reduced to the indicated dose. [See Drug Interactions (7.2) in the full prescribing information].

Hepatic Impairment: If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, the following dose reduction should be considered:

- For patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an initial dosing regimen of 400 mg in the morning and 200 mg in the evening (12 hours apart) per day followed by dose escalation to 400 mg twice daily based on patient tolerability should be considered. For patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 200 mg twice daily followed by a sequential dose escalation to 400 mg in the morning and 200 mg in the evening (12 hours apart) per day and then to 400 mg twice daily based on patient tolerability should be considered. [See Boxed Warning, Warnings and Precautions (5.9) and Use in Specific Populations (8.7) in the full prescribing information].

3 DOSAGE FORMS AND STRENGTHS

200 mg light yellow opaque hard gelatin capsules with a red axial imprint “NVR/TKI.”

4 CONTRAINDICATIONS

Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome. [See Boxed Warning].

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with Tasigna (nilotinib) can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Complete blood counts should be performed every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. [See Dosage and Administration (2)].

5.2 QT Prolongation

Tasigna has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner. [See Clinical Pharmacology (12.4) in the full prescribing information]. Prolongation of the QT interval can result in a type of ventricular tachycardia
called Torsade de pointes, which may result in syncope, seizure, and/or death. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated and following dose adjustments. [See Warnings and Precautions (5.2)]. Laboratory monitoring for patients receiving Tasigna may need to be performed more or less frequently at the physician’s discretion.

6 ADVERSE REACTIONS

The following serious adverse reactions can occur with Tasigna and are discussed in greater detail in other sections of this package insert. [See Boxed Warning, Warnings and Precautions (5)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the single open-label multicenter clinical trial, a total of 438 patients were treated (CML-CP = 318, CML-AP = 120).

The median duration of exposure in days for CML-CP and CML-AP patients was 245 (range 1-750) and 138 (range 2-1195), respectively. The median dose intensity of 797 mg/day (range 145-1149) was similar for both the chronic and accelerated phase patients and corresponded to the planned 400 mg twice daily dosing.

The median cumulative duration in days of dose interruptions for the CML-CP patients was 18 (range 1-165), and the median duration in days of dose interruptions for the CML-AP patients was 22 (range 1-163).

In CML-CP patients, the most commonly reported drug-related adverse reactions (≥10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia.

In CML-AP patients, the most commonly reported drug-related adverse reactions (≥10%) were rash, pruritus and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Sudden deaths and QT prolongation were reported. [See Boxed Warning and Warnings and Precautions (5.2 and 5.3)].

Discontinuation for drug-related adverse reactions was observed in 11% of CML-CP and 8% of CML-AP patients.

Table 4 shows the percentage of patients experiencing treatment-emergent adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in at least 10% of patients who received at least one dose of Tasigna are listed.

<table>
<thead>
<tr>
<th>Table 4. Treatment-Emergent Adverse Reactions Reported in ≥10% of Patients in the Clinical Study†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body System and Preferred Term</strong></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Edema, peripheral</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Bone pain</td>
</tr>
<tr>
<td>Muscle spasm</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
</tbody>
</table>

(continued)
Table 4. Treatment-Emergent Adverse Reactions Reported in ≥10% of Patients in the Clinical Study*  

<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>CML-CP N=318</th>
<th>CML-AP N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>CTC Grades 3/4 (%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td>16</td>
</tr>
</tbody>
</table>

* Excluding laboratory abnormalities  
* NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 5. Incidence of Clinically Relevant Grade 3/4 Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Hematologic Parameters</th>
<th>CML-CP N=318</th>
<th>CML-AP N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3/4*</td>
<td>Grades 3/4*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28%1</td>
<td>37%2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28%</td>
<td>37%3</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>23%</td>
</tr>
<tr>
<td>Elevated lipase</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Elevated bilirubin (total)</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Elevated SGPT (ALT)</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypornatriaemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Elevated SGOT (AST)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1 NCI Common Terminology Criteria for Adverse Events, version 3.0  
2 CML-CP: Thrombocytopenia: 11% were grade 3, 17% were grade 4  
3 CML-AP: Thrombocytopenia: 7% were grade 3, 30% were grade 4

6.2. Additional Data from Clinical Trials

The following drug-related adverse reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (1%–10%), and uncommon (0.1%–1%) adverse reactions single events are captured as unknown frequency. For laboratory abnormalities, very common events (>10%) not included in Table 4 are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

Infections and infestations: Common: pneumonia, urinary tract infection, gastroenteritis, pharyngitis.

Common: sepsis, bronchitis, herpes simplex, candidiasis,


Common: thrombocytosis, leukocytosis.

Endocrine Disorders: Common: hyperthyroidism.

Endocrine Disorders: Common: hyperthyroidism.

Metabolism and Nutrition Disorders: Common: hypomagnesemia, hyperkalemia, hyperglycemia, anorexia.

Common: hypokalemia, hypophosphatemia, dehydration, decreased appetite, increased appetite.

Common: diabetes mellitus, hypercalcaemia, hyperphosphatemia.

Psychiatric Disorders: Common: Insomnia.

Common: depression, anxiety.

Common: disorientation, confusional state.

Nervous System Disorders: Common: dizziness, paresthesia.

Uncommon: intracranial hemorrhage, migraine, tremor, hypothyroidism, hypothyroreosis.

Unknown frequency: brain edema, loss of consciousness, optic neuritis, periphereral neuropathy.

Eye Disorders: Uncommon: eye hemorrhage, visual acuity reduced, peri-orbital edema, conjunctivitis, eye irritation, dry eye.

Unknown frequency: papilloedema, diplopia, vision blurred, photophobia, eye swelling, blepharitis, eye pain.

Ear and Labyrinth Disorders: Common: vertigo.

Unknown frequency: hearing impaired, ear pain.

Cardiac Disorders: Common: palpitations, electrocardiogram QT prolonged.

Uncommon: cardiac failure, angina pectoris, atrial fibrillation, pericardial effusion, coronary artery disease, cardiomegaly, cardiac murmur, bradycardia.

Unknown frequency: myocardiad infarction, ventricular dysfunction, pericarditis, cardiac flutter, extrasosse.

Vascular Disorders: Common: hypertension, flushing.

Common: hypertension, hematoa, hematoa.

Unknown frequency: shock hemorrhagic, hypotension, thrombosis.

Respiratory, Thoracic and Mediastinal Disorders: Common: dyspnea, dyspnea exsitional, cough, dysphonia.

Uncommon: pulmonary edema, pleural effusion, interstitial lung disease, plethoric pain, pleurisy, epistaxis, pharyngolaryngeal pain, throat irritation.

Unknown frequency: pulmonary hypertension.

Gastrointestinal Disorders: Common: abdominal discomfort, dyspepsia, flatulence.

Uncommon: pancreatitis, gastrointestinal hemorrhage, melena, abdominal distension, mouth ulceration, gastroesophageal reflux, stomatitis, dry mouth.

Unknown frequency: gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematoma, gastric ulcer, esophagitis ulcerative, subileus.


Unknown frequency: hepatotoxicity, hepatomegaly, jaundice.

Skin and Subcutaneous Tissue Disorders: Common: night sweats, eczema, urticaria, alopecia, erythema, hyperhidrosis, dry skin.

Uncommon: exfoliative rash, ecchymosis, swelling face.

Uncommon: erythema nodosum, skin ulcer, petechiae, photosensitivity.

Musculoskeletal and Connective Tissue Disorders: Common: musculoskeletal chest pain, musculoskeletal pain.

Common: muscular weakness.

Unknown frequency: arthritis, joint swelling.

Renal and Urinary Disorders: Common: dysuria, micruriturs urgency, nocturia, polyuria.

Uncommon frequency: renal failure, hematuria, urinary incontinence.

Reproductive System and Breast Disorders: Uncommon: breast pain, gynecomastia, erectile dysfunction.

General Disorders and Administration Site Conditions: Common: pyrexia.

Unknown frequency: chest pain, face edema, gravitational edema, influenza-like illness, chills, malaise.

Investigations: Very common: lipase increased.

Common: blood amyloide increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood creatine blood phosphokinase increased, blood glucose increased, weight decreased, weight increased.

Uncommon: blood lactate dehydrogenase increased, blood glucose decreased, blood creatine increased, blood urea increased.

Uncommon frequency: troponin increased, blood potassium decreased, blood bilirubin unconjugated increased.

10 OVERDOSAGE

No cases of overdose have been reported. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

18 HOW SUPPLIED/STORAGE AND HANDLING

Tasigna (nilotinib) capsules are light yellow opaque hard gelatin capsules, size 0 with the red axial imprint "NVR/TKI". Tasigna capsules are supplied in blister packs.

Carton of 4 blister packs of 4(28) ............... NDC 0078-0526-67

Blister of 28 capsules .................................. NDC 0078-0526-51

Each blister pack contains one folded blister card of 28 capsules each, for dosing two in the morning and two in the evening at 12 hour intervals over a 7 day period.

Tasigna (nilotinib) Capsules, 200 mg, should be stored at 25°C (77°F); excursions permitted between 15°C-30°C (59°-86°F) [see USP Controlled Room Temperature].

Rev: August 2009

Manufactured by: Novartis Pharma Stein AG

Stein, Switzerland

©Novartis

Distributed by: Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936
Growing Risk or Growing Hope?

IN APL, STRATIFY FOR RISK

Risk stratification provides the advantage of decreasing toxicity for patients at low risk of relapse while allowing physicians to direct more aggressive therapy to those patients at high risk of relapse.

Please visit the NCCN Web site at www.NCCN.org for updated 2010 guidelines on treating APL.

Risk stratification: Helping improve outcomes in patients with acute promyelocytic leukemia (APL)

Kaplan-Meier Estimate of Relapse-Free Survival* According to the Risk Group Predictive Model

WBC and platelet counts are key to efficiently risk stratifying patients at diagnosis
- Presenting WBC and platelet counts at diagnosis consistently correlate with relapse risk
- A simple predictive model can be used to stratify patients with APL for risk of relapse

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>WBC count</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH RISK</td>
<td>&gt;10 x 10⁹/L</td>
<td>≤40 x 10⁹/L</td>
</tr>
<tr>
<td>INTERMEDIATE RISK</td>
<td>≤10 x 10⁹/L</td>
<td>≤40 x 10⁹/L</td>
</tr>
<tr>
<td>LOW RISK</td>
<td>≤10 x 10⁹/L</td>
<td>&gt;40 x 10⁹/L</td>
</tr>
</tbody>
</table>


Risk stratification provides the advantage of decreasing toxicity for patients at low risk of relapse while allowing physicians to direct more aggressive therapy to those patients at high risk of relapse.

In patients with APL
- Identify patients’ risk of relapse at diagnosis
- Choose the appropriate treatment for each patient according to risk of relapse

Please visit the NCCN Web site at www.NCCN.org for updated 2010 guidelines on treating APL.


©2010 Cephalon, Inc. All rights reserved.
Oncology May 2010 Printed in USA
Physicians understand that the latest cancer research doesn’t make an impact until it touches a patient. At UPMC Cancer Centers and the University of Pittsburgh Cancer Institute, our researchers work closely with oncologists to rapidly translate basic science into effective new cancer treatments. Our experts are nationally and internationally recognized for cutting-edge discoveries that are changing the landscape of oncology — including vaccines that block the progression of many cancers, new technologies that allow physicians to more precisely target treatments, and advances in minimally-invasive surgical procedures that are leading to reduced recovery times and better outcomes for patients. And through our multidisciplinary approach to care, medical, radiation, and surgical oncologists collaborate to develop individualized treatment plans that incorporate the most advanced cancer therapies tailored for each patient’s individual need. To learn more about treatment at UPMC Cancer Centers or research initiatives at the University of Pittsburgh Cancer Institute, call 1-800-533-UPMC or visit UPMCCancerCenters.com.
With CancerCare, the difference comes from:

• Professional oncology social workers
• Free counseling
• Education and practical help
• Up-to-date information
• CancerCare for Kids®

For needs that go beyond medical care, refer your patients and their loved ones to CancerCare. CancerCare’s free services help people cope with the emotional and practical concerns arising from a cancer diagnosis and are integral to the standard of care for all cancer patients, as recommended by the Institute of Medicine.

1-800-813-HOPE (4673)
www.cancercare.org
TRISENOX is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

**IMPORTANT SAFETY INFORMATION**

**WARNING (Abbreviated)**

**Experienced Physician and Institution:** TRISENOX (arsenic trioxide) injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia. **APL Differentiation Syndrome:** Some patients with APL treated with TRISENOX have experienced symptoms similar to a syndrome called the retinoic acid-acute promyelocytic leukemia (RA-APL), or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal. **ECG Abnormalities:** Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. **ECG and Electrolyte Monitoring Recommendations:** Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept above 4 mEq/L and magnesium concentrations should be kept above 1.8 mg/dL.

Serious adverse events, grade 3 or 4, were common. Those events attributable to TRISENOX in the phase 2 study of 40 patients with refractory or relapsed APL included QTc interval prolongation (n=16), APL differentiation syndrome (n=3), hyperleukocytosis (n=3), atrial dysrhythmias (n=2), hyperglycemia (n=2), and torsade de pointes (n=1).

Please see full BOXED WARNING and brief summary of full Prescribing Information on the following page.

**References:**

©2009 Cephalon, Inc. All rights reserved.
TRI-2009P-PM-00946 October 2009 Printed in USA.

For more information, visit [www.TRISENOX.com](http://www.TRISENOX.com).
BRIEF SUMMARY

See package insert for full prescribing information.

WARNING

Experienced Physician and Institution: TRISENOX (arsenic trioxide) injection should be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia.

APL Differential Diagnosis: Patients treated with TRISENOX have experienced symptoms similar to a syndrome called the tricholeukemia-Acute Promyelocytic Leukemia (RA-APL) or APL differentiation syndrome, characterized by fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions, with or without leukocytosis. This syndrome can be fatal to the patient. The management of the syndrome has not been fully studied. The disease has been associated with high-dose steroids and/or the use of the agent that is thought to cause it. The syndrome has been reported to occur more often in patients with RA-APL than in patients with APL who have not received arsenic trioxide or retinoic acid. The syndrome has been reported to occur more frequently in patients who were receiving retinoic acid and arsenic trioxide concomitantly than in patients who were receiving arsenic trioxide alone.

ECG Abnormalities: Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can occur when arsenic trioxide is administered either alone or in combination with other antileukemic drugs. ECG monitoring should be performed during the induction phase of therapy, and the QT interval should be corrected for heart rate, and for any other effects on the QT interval. The QT interval should be followed closely in all patients with RA-APL and APL who receive arsenic trioxide. If the QT interval is prolonged, concomitant administration of QT prolonging drugs should be avoided, and the QT interval should be monitored carefully. If the QT interval becomes greater than 500 msec, treatment with arsenic trioxide should be discontinued. For a complete list of adverse events occurring at a rate of 5% or more in clinical trials in 40 patients with APL who received TRISENOX at the recommended dose (0.15 mg/kg/day), refer to TRISENOX full prescribing information.

Electrolyte and Electrolyte Monitoring Recommendations: Prior to initiating therapy with TRISENOX, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium, and magnesium) should be assessed. Pre-existing electrolyte abnormalities should be corrected, and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QT greater than 500 msec, corrective measures should be completed and the QT reassessed with serial ECGs prior to considering using TRISENOX. During therapy with TRISENOX, potassium concentrations should be kept above 4.0 mg/dL. Hypomagnesemia should be kept above 1.5 mg/dL. Potassium levels with an associated QTc interval > 500...
2010 ASH STATE-OF-THE-ART SYMPOSIUM

Advances in Hematologic Malignancies and Thrombotic Disorders

SAVE THE DATE

SEPTEMBER 24-25, 2010
CHICAGO, IL
PALMER HOUSE HILTON

AMERICAN SOCIETY OF HEMATOLOGY

www.hematology.org/sas
THE LAURI STRAUSS LEUKEMIA FOUNDATION
Deadline: June 30, 2010

The Lauri Strauss Leukemia Foundation invites applications for Discovery research grants available to post doctoral fellows and junior faculty members interested in the field of Leukemia and Neoplastic hematopoietic disease research. The maximum award will be $45,000.00 with funding to begin January, 2011 for one year.

For application forms and further information call or e-mail the following: Grant office 516-781-4566; 516-767-1415; or e-mail: evherm@verizon.net; lslf@aol.com.
The American Society of Hematology (ASH) offers numerous free resources that are accessible online to hematology professionals around the world. Use them today:

Hematology: The ASH Education Program Book is published annually by ASH (one volume per year). It provides in-depth coverage of each Education Program session presented at the ASH annual meeting and summarizes the current state of clinical practice in hematology.

Explore latest issues online at www.hematology.org
> Publications > Hematology.

The ASH Teaching Cases are a reference tool for medical students and hematology instructors designed to simulate the steps involved in diagnosing a patient.

Refer to a case at www.hematology.org > Education & Careers > Teaching Cases.

The Hematologist, ASH’s bi-monthly member newsletter features information about ASH programs as well as the latest news in hematology.

Explore latest issues online at www.hematology.org
> Publications > The Hematologist.

Evidence-based Clinical Practice Guidelines are available on a number of topics for hematology practitioners.

Access guidelines online at www.hematology.org
> Policy and Practice > Resources for Practitioners > Guidelines.

The ASH Image Bank is a comprehensive reference and teaching tool. The images are presented as cases that are searchable and cross-referenced to other ASH educational resources.

Search images at www.ashimagebank.org.

Blood, the journal of the American Society of Hematology, is the most cited peer-reviewed publication in the field. It provides an international forum for the publication of original articles describing basic laboratory, translational, and clinical investigations in hematology. (Registration required, no cost.)

Some sections of the Blood journal, and all articles older than 12 months are available online for free.

Explore archived articles online at www.bloodjournal.org.

Blood: The Vital Connection is a newly created Web site that educates the general public about hematology and connects them to hematologists around the world.

Stay connected at www.bloodthevitalconnection.org.
Free *Blood* PDA Downloads and How to Use Them

**What are PDA downloads?** *Blood* PDA downloads are summaries of the latest *Blood* content sent directly to your Palm PDA or PocketPC PDA. The summaries consist of tables of contents, article abstracts, and full-text Inside *Blood* commentaries.

**Why use PDA downloads?** Use *Blood* PDA downloads if it is more convenient to review the latest *Blood* content on your PDA than on your computer. Full text of articles can be read on *Blood* Online or in print.

**What are the requirements for PDA downloads?** *Blood* PDA downloads work with the Palm operating system and the PocketPC 2002 operating system. They require a Macintosh or Windows computer with which you sync your PDA. You must register with HighWire Press (a free service), and you must download a small piece of software to your PDA via your desktop computer with which you sync your PDA.

**How do I set up my PDA?** Once you have registered with HighWire Press, follow the instructions to download the HW View software. Then sync your PDA with your desktop computer to download your *Blood* content.

**How do I get future content?** You must sync your PDA with your desktop computer each time you want the latest *Blood* content summaries. Then the summaries are on your PDA for your use away from your computer.
INDICATIONS AND USAGE

Control and Prevention of Bleeding Episodes

ADVATE is an antihemophilic factor (recombinant) indicated for control and prevention of bleeding episodes in adults and children with hemophilia A.

Perioperative Management

ADVATE is indicated in the perioperative management in adults and children with hemophilia A.

ADVATE is not indicated for the treatment of von Willebrand’s disease.

CONTRAINDICATIONS

Known anaphylaxis to mice or hamster protein or other constituents of the product.

WARNINGS AND PRECAUTIONS

Genetic

The clinical response to ADVATE may vary, if bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of ADVATE should be administered to achieve a satisfactory clinical response. If the patient’s plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected time, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed.

Anaphylaxis and Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible and have been reported with ADVATE. Symptoms have manifested as dizziness, pallor, rash, flushing, face swelling, urticaria, dyspnea, and pruritus.

ADVATE contains trace amounts of mouse immunoglobulin G (specific, maximum of 0.1 mg/kg ADVATE) and hamster (CHO) proteins (maximum of 1.5 mg/kg ADVATE). Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Discourage ADVATE if hypersensitivity symptoms occur and administer emergency treatment.

Neutralizing Antibodies

Patients treated with AHT products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of ADVATE predominantly in previously untreated patients (PUP) and previously minimally treated patients (PMTP). If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with the expected dose of ADVATE, use isotestradiol (EST) to titrate inhibitors.

● Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated.

● Monitor for development of factor VIII inhibitors. Perform the Bethesda assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of ADVATE, use isotestradiol (EST) to titrate inhibitors.

● If the inhibitor is less than 10 IU per ml, the administration of additional antihemophilic factor concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response. Adequate hemostasis may not be achieved if inhibitor titers are above 10 IU per ml. The inhibitor titer may rise following ADVATE infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

ADVERSE REACTIONS

The most serious adverse drug reactions (ADRs) seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.

The most common ADRs observed in clinical trials (frequency > 2% of subjects) were: factor VIII inhibitor formation observed predominantly in PUPs and headache (6.1)

Clinical Trial Experience

because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

ADVATE has been evaluated in five completed studies in previously untreated patients (PUPs) and one ongoing study in PUPs with severe to moderately severe hemophilia A (factor VIII ≥ 2% of normal). A total of 234 subjects have been treated with ADVATE as of March 2006. Total exposure to ADVATE was 6,453,794 IU (derived from 47 IU/kg in 44,926 infusions. The median duration of participation per subject was 270.5 hours (range 1 to 2,266 days) and the median exposure to ADVATE per subject was 128.0 hours (range 1 to 598 days).

There were 2,507 adverse events (AEs) reported in 215 subjects. None of the subjects withdrew from the studies due to adverse events. There were no deaths. Nineteen treated subjects reported no AEs during their participation. The most common AEs (product-related and unrelated, according to the investigator’s opinion) occurring in at least 5% of subjects who received at least 1 ADVATE study infusion are shown in Table 1.

The majority of the events in Table 1 appear to have been related to trauma, intercurrent mild or respiratory or gastrointestinal disease or well-described complications of hemophilia.

The most common ADRs with a frequency greater than or equal to 2% are shown in Table 2. Of all ADRs, none were reported in neonates, 16 were reported in infants, 7 were reported in children, 8 were reported in adolescents and 25 were reported in adults.

IMMUNOGENICITY

The development of factor VIII inhibitors with the use of ADVATE was evaluated in clinical studies with pediatric PTPs (<6 years of age) and PTP (>6 years of age) with ≥10 factor VIII inhibitor exposures. Of 186 subjects who were treated for at least 10 exposure days or on study for a minimum of 120 days, 1 adult developed a low-titer inhibitor (0.2 IU) in the Bethesda assay after 26 exposure days.

Eight weeks later, the inhibitor was no longer detectable, and no recovery was noted. Fourteen of these 10 showed an upward trend in anti-mu IgG antibodies. 182 treated subjects have been monitored for anti-mu Igs to heterologous factor VIII for >6 months.

The mean age of patients who have been treated with ADVATE as of March 2006 is 17 years.

Some of these subjects had numerous infections, and some had a history of allergy. Of these subjects had numerous repeat exposures to the study product without recurrence of the events and a causal relationship between the antibody findings and these clinical events has not been established.

Of the 181 subjects who were treated and assessed for the presence of anti-human von Willebrand factor (VWF) antibodies, none displayed laboratory evidence indicative of a positive serologic reaction.

Post Marketing Experience

The following adverse reactions have been identified during post approval use of ADVATE. 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.

Among patients treated with ADVATE, cases of serious allergic/ hypersensitivity reactions including anaphylaxis have been reported and factor VIII inhibitor formation observed predominantly in PUPs. Table 3 represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Baxter Healthcare Corporation

1060138

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-UPDATE (1-888-877-3238)

Baxter, Advate, Recombinant and Recombinate are trademarks of Baxter International Inc. Baxter, Advate and Recombinate are registered in the U.S. Patent Office.
In recombinant FVIII therapy...

...ADVATE is a complete package

- **Pathogen safety** — ADVATE is the only recombinant FVIII therapy that is full-length and free of blood-based additives. Because no blood-derived components are added at any stage of the manufacturing process, the potential risk of pathogens that may be carried in blood-based additives is eliminated.

  There have been no confirmed reports of viral transmissions with recombinant FVIII therapies.1

- **Efficacy** — 93% of bleeds managed with 1 or 2 infusions in a clinical study.2

  "Pivotal study of 108 PTPs with FVIII ≤2%."

- **Low rate of inhibitor development** — in completed clinical studies, <1% of previously treated patients (PTPs) developed an inhibitor.3

  The development of inhibitors has been detected in patients receiving ADVATE.

ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] is indicated for control and prevention of bleeding episodes in adults and children with hemophilia A and for perioperative management in adults and children with hemophilia A.

ADVATE is not indicated for the treatment of von Willebrand’s disease.

**Important Risk Information for ADVATE therapy**

ADVATE is contraindicated in patients with known anaphylaxis to mouse or hamster proteins or other constituents of the product.

- Allergic-type hypersensitivity reactions, including anaphylaxis, are possible and have been reported with ADVATE. Symptoms have manifested as dizziness, paresthesia, rash, flushing, face swelling, urticaria, dyspnea, and pruritus. Discontinue use if hypersensitivity symptoms occur and administer appropriate emergency treatment.

- Patients treated with AHF products should be monitored following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs)

- If expected plasma factor VIII levels are not attained, or if bleeding is not controlled with an expected dose, test for the presence of inhibitors.

- The most serious adverse reactions seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to factor VIII.

- The most common adverse reactions observed in clinical trials (frequency ≥2% of subjects) were factor VIII inhibitor formation (observed predominantly in PUPs) and headache.

Please see US brief summary of Prescribing Information on adjacent page.

Licenses and licensing conditions may vary from country to country; therefore, please always consult your local full Prescribing Information.

**References:**


Baxter, Advate, and Baxject are trademarks of Baxter International Inc.

© Copyright (January 2010), Baxter Healthcare Corporation. All rights reserved. Printed in the U.S.A. HYL5133