Investigating Everolimus* in Diffuse Large B-cell Lymphoma

Study Description
Phase III, double-blind study in poor-risk patients with diffuse large B-cell lymphoma (DLBCL) following complete response to rituximab-containing chemotherapy

Study Design†

**Primary Endpoint**
Disease-free survival

For more information
- Call 1-800-340-6843 (United States only)
- Visit www.thewideprogram.com
- Contact your local Novartis Medical Science Liaison

*This is an investigational study; there is no guarantee that everolimus will become commercially available for this indication.*
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No Good Cancer
Hodgkin lymphoma—
≈10% refractory rates¹
≈30% relapse rates after complete response¹
≈50% of transplants fail²,³
Long-term health complications⁴
Reduced survival in some patients initially cured⁵

References
NOW ENROLLING PATIENTS WITH POLYCYTHEMIA VERA

RESPONSE
Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor Ruxolitinib Versus Best Available Care

A PHASE III STUDY INVESTIGATING RUXOLITINIB—AN ORAL JAK1 AND JAK2 INHIBITOR

The RESPONSE trial is a global, randomized, open-label, multicenter, phase III study of the oral JAK1 and JAK2 inhibitor ruxolitinib, formerly known as INCB018424, in patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea. RESPONSE is sponsored by both Incyte and Novartis.

Primary endpoint
Composite endpoint of phlebotomy independence and spleen volume reduction at Week 32

Secondary endpoints
• Proportion of patients who maintain the primary endpoint response for ≥48 weeks
• Proportion of patients achieving complete hematologic remission at 32 weeks

Patients with PV (N=300)

Randomized 1:1

Ruxolitinib (oral) 10 mg bid

Best available therapy as selected by physician*

Best available therapy as selected by physician†

If you have a PV patient who is at least 18 years of age and who meets the following criteria, he/she may be eligible for enrollment in RESPONSE:

• Resistant to or intolerant of hydroxyurea
• Phlebotomy requirement due to inadequate hematocrit control at least once every 3 months
• Palpable splenomegaly ≥5 cm below the costal margin
• Elevated white blood cell and/or platelet counts

To enroll a US patient in RESPONSE or to find out more about this trial, please call 1-877-4-PV-TRIAL or visit www.responsetrial.com.

Ruxolitinib is an investigational compound. Its efficacy and safety have not been established. There is no guarantee that this compound will become commercially available.
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A multicenter phase I trial to assess the safety profile of the CD30-directed antibody-drug conjugate brentuximab vedotin (SGN-35) in treatment-naïve systemic ALCL patients when administered sequentially and concurrently with multi-agent chemotherapy.

Key Inclusion Criteria

- Treatment-naïve systemic ALCL patients
  - ALK negative disease, any IPI score
  - ALK positive disease, IPI score ≥2
- Histologically confirmed diagnosis of CD30-positive systemic ALCL
- ECOG performance status of 0 to 2
- Adequate organ function

For key inclusion and exclusion criteria, please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01309789); contact Seattle Genetics at 866-333-7436 (US only) or e-mail clinicaltrials@seagen.com.

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TREANDA® is his chemo. 
This is his therapy.
TREANDA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first-line therapies other than chlorambucil has not been established.

Selected Safety Information

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur.

- Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment. Myelosuppression is frequently severe and should be expected when treating patients with TREANDA.

- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA.

TREANDA was compared with chlorambucil in a randomized, open-label, phase 3 trial in treatment-naive patients with Binet stage B or C (Rai stages I-IV) CLL who required treatment (N=301). Patients were scheduled to receive either TREANDA 100 mg/m² intravenously on Days 1 and 2 (n=153) or chlorambucil 0.8 mg/kg orally on Days 1 and 15 (n=148) of a 28-day treatment cycle, up to 6 cycles.

TREANDA was generally well tolerated in the pivotal phase 3 trial.

The most common non-hematologic adverse reactions (frequency ≥15%) were pyrexia (24%), nausea (20%), and vomiting (16%) (n=153). The most common hematologic abnormalities (frequency ≥15%) were anemia (89%), thrombocytopenia (77%), neutropenia (75%), lymphopenia (68%), and leukopenia (61%) (n=150).

* TREANDA (95% CI: 11.7, 23.5) vs chlorambucil (95% CI: 5.6, 8.6).
† HR=hazard ratio.
‡ CI=confidence interval.

TREANDA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first-line therapies other than chlorambucil has not been established.
The Grade 3 and 4 hematologic laboratory test values by treatment group in the randomized CLL clinical study are described in Table 3. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

Table 2: Incidence of Hematologic Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>92 (61)</td>
<td>0</td>
<td>31 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>134 (89)</td>
<td>20 (13)</td>
<td>92 (62)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>116 (77)</td>
<td>16 (11)</td>
<td>110 (78)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Lymphocytes Decreased</td>
<td>92 (61)</td>
<td>42 (28)</td>
<td>26 (16)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Neutrophils Increased</td>
<td>110 (72)</td>
<td>70 (47)</td>
<td>47 (31)</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

In the randomized CLL clinical study, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 1% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that significant deterioration does not occur. Post-Marketing Experience. The following adverse reactions have been identified during post-marketing experience with TREANDA. These reactions are reported voluntarily from a population of uncertain size; it is therefore not always possible to reliably estimate their frequency or establish a causal relationship to drug therapy or product use, relate incidence to exposure, or identify the exact relationship of the reaction to drug therapy. Infections. Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The administration of allopurinol should be delayed or discontinued. Other Malignancies. There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchiolitis. The association with these malignancies has not been determined. Extramedullary B cell Neoplasms. There are post-marketing reports of extramedullary presentations of histologically normal in lymphomas resulting in hospitalizations from ehrlichia, marked swelling, and pain. Precautions should be used to avoid extravasations, including monitoring of the intravenous infusion site for any irritation. Symptoms include pain at the injection site. Monitor and treat for any signs of extravasation.

Table 1: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in At Least 5% of Patients

<table>
<thead>
<tr>
<th>System organ class</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>121 (79)</td>
<td>52 (34)</td>
<td>96 (67)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (20)</td>
<td>1 (1)</td>
<td>21 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>1 (1)</td>
<td>9 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>5 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Infection and infestations

<table>
<thead>
<tr>
<th>System organ class</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>31 (20)</td>
<td>1 (1)</td>
<td>21 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>1 (1)</td>
<td>9 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>5 (3)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>121 (79)</td>
<td>52 (34)</td>
<td>96 (67)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (24)</td>
<td>6 (4)</td>
<td>8 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>8 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Meticulous</td>
<td>6 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompetence defects</td>
<td>7 (5)</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>10 (7)</td>
<td></td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (6)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>6 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>11 (7)</td>
<td></td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Metabolic and nutrition disorders</td>
<td>11 (7)</td>
<td></td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>11 (7)</td>
<td></td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary and mediastinal disorders</td>
<td>6 (4)</td>
<td>1 (1)</td>
<td>7 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Metabolic and nutrition disorders</td>
<td>12 (8)</td>
<td></td>
<td>4 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (5)</td>
<td></td>
<td>2 (1)</td>
<td></td>
</tr>
</tbody>
</table>
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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 allergy to mouse or hamster protein or other constituents of the above.

WARNINGS AND PRECAUTIONS
General
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. If 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 delay 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, paresthesias, rash, flushing, face swelling, urticaria, dyspnea, and pruritus.

ADVATE contains trace amounts of mouse immunoglobulin M (specific maximum 0.1 ng/mL) ADVATE and hamster (CHO) proteins (maximum of 1.5 mg/mL ADVATE). Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins. Discontinue ADVATE if hypersensitivity symptoms occur and administer appropriate emergency treatment.

Neutralizing Antibodies
Patients treated with A/H 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 (PUPs) and previously minimally treated patients (MTPs). If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed.

Monitoring Laboratory Tests
• 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 Bethesda Units (BU) to inhibitor titers.
  • If the inhibitor is less than 10 BU 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 BU per mL. The inhibitor titers 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 (0.1).

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 observed 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 treated patients (PTPs) 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 4,539,784 IU (derived from 47 doses) in 44,926 infusions. The median duration of participation per subject was 370.5 days (range: 1 to 1,256) days and the median exposure to ADVATE per subject was 128.0 (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 respiratory or gastrointestinal disease or well-described complications of the disease.

Fifty-six ADRs were reported in 27 subjects. Nearly all (53/56) were isolated events or occurred once in one subject with numerous subsequent infusions without recurrence. The most common AEs 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 (<5 years of age with >50 factor VIII exposures) and PTPs (10 years of age with >150 factor VIII exposures). Of 198 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 BU) in the Bethesda assay after 26 exposure days.

Eight weeks later, the inhibitor was no longer detectable, and in vivo recovery was normal and stable. Five of the other 197 subjects continued to receive ADVATE in nonrandomized studies. Immunoassay testing for inhibitors was performed on 64 subjects, and in vivo recovery was normal in all cases tested.

ADVERSE HEMOSTATIC RESPONSE
In clinical studies that enrolled previously untreated subjects identified as having had up to 3 exposures to a factor VIII product at the time of enrollment, 5 (20%) of 25 subjects who received ADVATE developed neutralizing inhibitors to FVIII. Four patients developed high titer (>99.9%) inhibitor and one patient developed low-titer inhibitors. Inhibitors were detected at a median of 11 exposure days (range 7 to 13 exposure days) to investigational product. Immunogenicity was also evaluated by measuring the development of antibodies to heterologous proteins. 182 treated subjects were screened for anti-ADVATE antibody and 170 were negative.

Of these 10 showed an upward trend in antibody titer over time and 4 showed sustained but transient elevations of antibodies. 162 treated subjects were assessed for anti-muHGH antibodies. 2 showed sustained but transient elevations of antibodies. Four subjects who demonstrated antibody elevations reported isolated events of urticaria, pruritus, rash, and slightly elevated eosinophil counts. All 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 response.

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.

Table 1. Adverse Events Reported by > 5% of Subjects

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Subjects</th>
<th>Percent of Subjects</th>
</tr>
</thead>
</table>
| Ear and labyrinth disorders | 17 | 14.0%
| Gastrointestinal disorders | 16 | 12.5%
| Hemorrhagic disorders | 20 | 16.1%
| General disorders and administration site conditions | 17 | 13.0%
| Infections and infestations | 19 | 15.4%
| Nervous system disorders | 25 | 20.2%
| Respiratory, thoracic and mediastinal disorders | 50 | 37.8%
| Skin and subcutaneous tissue disorders | 20 | 15.8%

* Includes data from 23 treatments from 5 completed studies in PTPs, and 1 ongoing study in PUPs as of 27 March 2006.

Table 2. Summary of Most Common Adverse Drug Reactions (ADRs) with a Frequency >= 2%

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Number of Subjects</th>
<th>Percent of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII inhibitor</td>
<td>5</td>
<td>2.14%</td>
</tr>
</tbody>
</table>

* ADR = Adverse Drug Reaction; *number events considered by the investigator to be at least possibly related to administration of this product.

Table 3. Post-Marketing Experience

<table>
<thead>
<tr>
<th>Organ System</th>
<th>MedDRA Preferred Term</th>
<th>ADR Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction</td>
<td>0.6%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Factor VIII inhibition</td>
<td>0.5%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site reaction</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

* These reactions have been manifested by dizziness, paresthesias, rash, flushing, face swelling, urticaria, and pruritus.
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.7
  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.1
  Pivotal study of 108 PTPs with FVIII ≥7%.
- **Low rate of inhibitor development** — in completed clinical studies, <1% of previously treated patients (PTPs) developed an inhibitor.5,6
  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 for the development of factor VIII inhibitors. Inhibitors have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs).

- **Convenience** — broad selection of dosage strengths (250 to 3000 IU), short infusion time (up to 10 mL/min), BAXJECT II device, and room temperature storage for up to 6 months.2
- **Commitment** — patient support programs and healthcare professional (HCP) collaboration to stay at the forefront of hemophilia care
  1 In clinical studies, ADVATE therapy demonstrated a low inhibitor rate with an overall incidence rate of 0.51% (95% confidence interval [CI], 0.03%-2.91%).1
  2 Up to 30°C/86°F, not to exceed printed expiration date. After storage at room temperature, ADVATE must not be returned to the refrigerator. Two-year shelf life if refrigerated.1

- 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.

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