Coagulation Factor IX (Human) AlphaNine® SD

The ability of the AlphaNine SD process to eliminate virus, by physically partitioning virus from product, was evaluated at key stages of the manufacturing process. Studies were performed using a lipid-embedded model virus (Sindbis) and non-lipid model viruses (porcine parvovirus, encephalomyocarditis virus, and reovirus). Known amounts of different viruses (as measured by virus antigen capture and reverse transcriptase assays) were added to product samples. In an ongoing efficacy and safety study of 26 patients, no subjects tested positive (as measured by virus antigen capture and reverse transcriptase assays). In addition, this process was shown to be effective in reducing the risk of infection. Therefore, the developer should weigh the risks and benefits of the use of this product and should discuss these with the patient.

CONTRAINdications

SAFETY

Side effects are not known. However, the occurrence of adverse reactions to the administration of blood or blood products has been established. In the clinical study that compared the in vivo half-life and recovery of AlphaNine SD and HT products, no adverse events were associated with 18 infusions of AlphaNine SD administered to 18 individuals with severe to moderate hemophilia B. The administration of plasma preparations may cause allergic reactions, including fever, urticaria, rash, pruritus, flushing, angioedema, bronchospasm, hypotension, and circulatory collapse. Patients should be informed of the early symptoms and signs of hypersensitivity reactions, including urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections resulting from the transfer of infectious agents. Anaphylactic and anaphylactoid reactions may occur to any component of the preparation. The physician should be prepared to treat acute hypersensitivity reactions. In an on going efficacy and safety study of 26 patients, no subjects tested positive (as measured by virus antigen capture and reverse transcriptase assays). In addition, this process was shown to be effective in reducing the risk of infection. Therefore, the developer should weigh the risks and benefits of the use of this product and should discuss these with the patient.

PRECAUTIONS

Animal reproduction studies have not been conducted with AlphaNine SD. It is also not known whether AlphaNine SD can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AlphaNine SD should not be administered at a rate exceeding 10 mL/minute. Rapid administration may result in vasoconstrictive reactions, including anaphylaxis, with anaphylactic and anaphylactoid reactions occurring to any component of the preparation. The physician should be prepared to treat acute hypersensitivity reactions. In an on going efficacy and safety study of 26 patients, no subjects tested positive (as measured by virus antigen capture and reverse transcriptase assays). In addition, this process was shown to be effective in reducing the risk of infection. Therefore, the developer should weigh the risks and benefits of the use of this product and should discuss these with the patient.

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patient received approximately 15,000 IU (range 3,295 to 52,200 IU Factor IX) in an average of 16 infusions (range 2 to 26 infusions). Results from this study showed no bleeding episodes during the course of postsurgery therapy. There was no hematological evidence (measured by hematocrit, peripheral thromboplastin time, prothrombin time, thromboplastin time, D-dimers and platelet counts) of thrombogenicity.12 To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSE AND ADMINISTRATION

For adult usage:

AlphaNine SD should be administered intravenously immediately following reconstitution. Administration of AlphaNine SD within three hours after reconstitution is recommended to avoid the potential ill effect of any inadvertent bacterial contamination occurring during reconstitution. Discard any unused contents into the appropriate safety container.

Each vial of AlphaNine SD is labeled with the total units expressed as International Units (IU) of Factor IX, which is referenced to the WHO International Standard. One unit approximates the activity in one mL of pooled normal human plasma.

The amount of AlphaNine SD required to establish hemostasis will vary with each patient and depend upon the circumstances. The following formula may be used as a guide in determining the number of units to be administered:13

\[
\text{Body weight (kg)} \times \text{Factor IX} \times 1.0 \text{ IU/kg} = \text{Factor IX Required (IU)}
\]

Example:

70 kg \times 1.0 \text{ IU/kg} = 2,800 IU AlphaNine SD

In clinical practice there is variability between patients and their clinical response. Therefore, the Factor IX level of each patient should be monitored frequently during replacement therapy.

For pediatric usage: See PRECAUTIONS

Treatment Guidelines for Hemorrhagic Events and Surgery in Patients Diagnosed with Hemophilia B

<table>
<thead>
<tr>
<th>Type of Hemorrhage or Surgical Procedure</th>
<th>Examples</th>
<th>Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Hemorrhages</td>
<td>Bruises, cuts or scrapes, uncomplicated joint hemorrhage</td>
<td>FIX levels should be brought to at least 20-30% (20-50 IU FIX/kg/twice daily) until hemostasis is achieved (1-2 days).</td>
</tr>
<tr>
<td>Moderate Hemorrhages</td>
<td>Nose bleeds, mouth and gum bleeds, dental extractions, hematuria</td>
<td>FIX levels should be brought to 25-50% (25-50 IU FIX/kg/twice daily) until hemostasis has been achieved (2-7 days, on average).</td>
</tr>
<tr>
<td>Major Hemorrhages</td>
<td>Joint and muscle hemorrhages (especially in the large muscles), major trauma, hematuria, intracranial bleeding</td>
<td>FIX levels should be brought to 50% for at least 3-5 days (30-50 IU FIX/kg/twice daily). Following this treatment period, FIX levels should be maintained at 20% (20 IU FIX/kg/twice daily) until hemostasis has been achieved. Major hemorrhages may require treatment for up to 10 days.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Prior to surgery, FIX should be brought to 50-100% of normal (50-100 IU FIX/kg/twice daily). For the next 7 to 10 days, or until healing has been achieved, the patient should be maintained at 50-100% FIX levels (50-100 IU FIX/kg/twice daily).</td>
<td></td>
</tr>
</tbody>
</table>

Dosing requirements and frequency of dosing is calculated on the basis of an initial response of 1% FIX increase achieved per h if FIX infused per kg body weight and an average half-life for FIX of 16 hours. If dosing studies have revealed that a particular patient exhibits a lower response, the dose should be adjusted accordingly.

For pediatric usage: See PRECAUTIONS

RECONSTITUTION

See Aseptic Technique

RECONSTITUTION

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HOW SUPPLIED

AlphaNine SD is supplied in sterile, lyophilized form in single dose vials accompanied by 10 mL diluted (Sterile Water for Injection [USP]) Factor IX activity standardized in International Units (IU) which is referenced to the WHO International Standard, is stated on the label of each concentrate vial. AlphaNine SD is packaged with a Mix2Vial filter transfer set for use in administration. It is available in the following potencies, and the product is also color coded based upon essay on the carton and vial label as follows:

<table>
<thead>
<tr>
<th>Potency</th>
<th>NDC</th>
<th>Essay Color Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 IU FIX single dose vial</td>
<td>68616-1601-2</td>
<td>1000 IU FIX Range – blue box</td>
</tr>
<tr>
<td>1000 IU FIX single dose vial</td>
<td>68616-3602-2</td>
<td>1500 IU FIX Range – red box</td>
</tr>
<tr>
<td>500 IU FIX/10 mL single dose vial</td>
<td>68616-3603-2</td>
<td>2500 IU FIX Range – black box</td>
</tr>
</tbody>
</table>

REFERENCES

2. Data on file at Grifols Biopharmaceuticals Inc.