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OVERDOSAGE

Although limited data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.

DESCRIPTION

BabyBIG, Botulism Immune Globulin Intravenous (Human) (BIG-IV), is a solution obtained by controlled precipitation and subsequent purification of immunoglobulin G (IgG), stabilized with 5% sucrose and 1% albumin (human). It contains no preservatives. The purified immunoglobulin is derived from pooled adult plasma from persons who were immunized against Clostridium botulinum toxin and selected for their high titer of neutralizing antibody against botulinum neurotoxins type A and B. All donors were tested and prior testing found to be negative for antibodies against the human immunodeficiency virus and the hepatitis B and hepatitis C viruses.

The pooled plasma was fractionated by cold ethanol precipitation of the proteins according to the Cohn/Ockley method, modified to yield a product suitable for intravenous administration. Several steps in the manufacturing process have been validated for their ability to inactivate or remove viruses that may not have been detected in the Source Plasma.

These include Cohn/Ockley fractionation (Fraction I through Supernatant III filtrate); nanofiltration through 35- and 25-nm filters; and sodium and solvent/detergent viral inactivation. These viral reduction steps have been validated in a series of in vitro experiments for their capacity to inactivate and/or remove Human Immunodeficiency Virus type 1 (HIV-1) and the hepatitis C virus model viruses: bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus, mouse encephalomyelitis virus (MVM) as a model for hepatitis A virus, and pseudorabies virus (PRV), feline calicivirus (FCV), and Sindbis virus to cover a wide range of physicochemical properties in the model viruses studied. Total mean log reductions range from 4.63 to greater than 16 log_10, as shown in the following table.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo*</th>
<th>BabyBIG Lot 1</th>
<th>BabyBIG Lot 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>9(14)</td>
<td>3(5)</td>
<td>9(14)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4(6)</td>
<td>3(4)</td>
<td>3(4)</td>
</tr>
<tr>
<td>Headache</td>
<td>3(5)</td>
<td>4(6)</td>
<td>5(8)</td>
</tr>
<tr>
<td>Fungal Infection</td>
<td>2(3)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6(9)</td>
<td>8(12)</td>
<td>9(14)</td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5(8)</td>
<td>6(9)</td>
<td>6(9)</td>
</tr>
<tr>
<td>Rash</td>
<td>3(5)</td>
<td>5(8)</td>
<td>5(8)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>2(3)</td>
<td>1(2)</td>
<td>2(3)</td>
</tr>
<tr>
<td>Reaction to vial</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0(0)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>URI</td>
<td>4(6)</td>
<td>5(8)</td>
<td>5(8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6(9)</td>
<td>9(14)</td>
<td>9(14)</td>
</tr>
</tbody>
</table>

* Included hydrophobic chromatography after solvent/detergent treatment.

Additional testing performed with bovine parvovirus (as a model for parvovirus B19) showed, a mean cumulative reduction factor of greater than 7.3 log_10 for Cohn/Ockley fractionation and solvent/detergent treatment followed by hydrophobic chromatography. A mean cumulative reduction factor of 2.55 log_10 was observed for removal of porcine parvovirus by nanofiltration.

When reconstituted with Sterile Water for injection USP, each cubic centimeter (ml) contains approximately 50 ± 10 mg immunoglobulin, primarily IgG, and trace amounts of IgM and IgA. 50 mg contains 10 mg albumin (human); and approximately 20 ± 10 mg sodium.

The reconstituted solution should appear colorless and translucent. The product is stabilized with 5% sucrose and 1% albumin (human). The solution contains no preservative.

Pharmacodynamics

Mean Reduction Factor (log10)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Placebo*</th>
<th>BabyBIG Lot 1</th>
<th>BabyBIG Lot 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sindbis</td>
<td>8.0</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>HIV-1</td>
<td>4.5</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>PRV</td>
<td>14.7</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>BVDV</td>
<td>7.3</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>MEMV</td>
<td>10.3</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>FCV</td>
<td>10.5</td>
<td>1.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>

The half-life of injected BabyBIG has been shown to be approximately 28 days in infants, which is in agreement with existing data for other immunoglobulin preparations [14].

CLINICAL STUDIES

Two clinical studies in infant botulism were performed: (1) an adequate and well-controlled study to evaluate the safety and efficacy of BabyBIG (N=129), and (2) on open label study to collect additional safety data and to confirm efficacy (N=293). In the adequate and well-controlled clinical study, BabyBIG, given within the first 4 days of hospital care to infants with laboratory-confirmed infant botulism, has been shown to reduce the following:

- Mean Length of Hospital Stay in Weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo*</th>
<th>BabyBIG Lot 1</th>
<th>BabyBIG Lot 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Length of Stay</td>
<td>16.0</td>
<td>9.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Length of hospital stay was also analyzed by patient age in both the adequate and well-controlled study and in an open label study.

OVERNIGHT STAY

In the open label study only, the following adverse events occurred in at least 5% of the patients:

- Anemia
- Fatigue
- Headache
- Gastrointestinal
- Meningoencephalitis
- Nausea
- Reaction to vial
- URI
- Vomiting

Adverse event coding was used in the open label study to distinguish minor clinical events that required no intervention and more significant events that required intervention. For example, "increased blood pressure" or "decreased blood pressure" was assigned when transient changes in blood pressure were observed, whereas "hypertension" or "hypotension" was assigned when more prolonged or significant changes were observed.

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.

Experience with BabyBIG. No adverse reactions have been identified or reported that are ascribed to the use of BabyBIG during postapproval use. Retrospective publications have shown similar safety-related information consistent with the safety-related information in the approved product labeling, and no new safety-related information has been presented for BabyBIG [15-17].

Experience with Other IGIV Products. Some classes of adverse reactions that have not been reported in BabyBIG clinical studies or postmarketing experience have been observed with the other post-approval use of other IGIV products, as shown in the following table.

Drugs Interactions

Admixtures of BabyBIG with other drugs have not been evaluated. It is recommended that BabyBIG be administered separately from other drugs or medications that the patient may be receiving [see DOSAGE AND ADMINISTRATION (2)].

Procedures

Antibodies present in immune globulins may interfere with the immune response to live virus vaccines such as polio, measles, mumps, and rubella; therefore, vaccination with live virus vaccines should be deferred until at least 6-12 months after administration of BabyBIG. If such vaccinations were given shortly before or after BabyBIG administration, revaccination may be necessary.

USE IN SPECIFIC POPULATIONS

Pediatric Use

BabyBIG has been studied for safety and efficacy only in patients below one year of age [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14)]. It has not been tested in other populations.

References

1. Cytogam®. Approved product labeling, and no new safety-related information has been presented for BabyBIG [15-17].

2. Admixtures of BabyBIG with other drugs have not been evaluated. It is recommended that BabyBIG be administered separately from other drugs or medications that the patient may be receiving [see DOSAGE AND ADMINISTRATION (2)].

3. Antibodies present in immune globulins may interfere with the immune response to live virus vaccines such as polio, measles, mumps, and rubella; therefore, vaccination with live virus vaccines should be deferred until at least 6-12 months after administration of BabyBIG. If such vaccinations were given shortly before or after BabyBIG administration, revaccination may be necessary.

4. USE IN SPECIFIC POPULATIONS

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