FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 Preparation for Administration
   2.2 Treatment of Infant Botulism Caused by Type A or B
   2.3 Administration
   3 DOSAGE FORMS AND STRENGTHS
   4 CONTRAINDICATIONS
   5 WARNINGS AND PRECAUTIONS
   6 ADVERSE REACTIONS
   7 USE IN SPECIFIC POPULATIONS
   8 OVER Dosage
   9 DESCRIPTION
   10 CLINICAL PHARMACOLOGY
   11 CLINICAL STUDIES
   12 REFERENCES
   13 HOW SUPPLIED/STORAGE AND HANDLING
   17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BabyBIG (Botulinum Immune Globulin Intravenous (Human) (BIG-IV)) Lymphoprep Powder for Reconstitution and Injection

Initial U.S. Approval: 2003

1.1 INDICATIONS AND USAGE

BabyBIG is an immune globulin intravenous (human) indicated for:

• Treatment of infant botulism caused by type A or B in infants below one year of age.

2 DOSAGE AND ADMINISTRATION

For Infantile Use Only

2.1 Preparation for Administration

• Reconstitute the lyophilized product, the vial shall be entered only once for the purpose of administration, and the infusion solution shall be used within 2 hours of reconstitution.

• Remove the tip of the vial and clean the rubber stopper with 70% ethanol.

• Reconstitute the lyophilized product with 2 mL of sterile water for injection use, to obtain a 5% solution.

• A double-ended transfer needle or large syringe is suitable for adding the water for reconstitution. When using a double-ended transfer needle, insert one end first into the vial of the lyophilized product to suspend it in an evacuated vial, therefore, the solution transfer should be facilitated by sucking the jet of air should be aimed to the side of the vial.

2.2 Treatment of Infant Botulism Caused by Type A or B

The recommended total dosage of BabyBIG is 1.0-1.5 mg/kg (50 mg/mL) given as a single dose in infants with the use of less licensed Biotherapies, those that contained a staphylococcal and were administered at daily doses of a minimum rate of 0.5 mL/kg/h. The recommended total dosage is the entire course of therapy. BabyBIG contains serum that is a stabilizing for patients that may develop anaphylactic shock of IgG levels and should be used in consultation with a pediatrician, infectious disease specialist, diabetes mellitus, sepsis, septic shock, or who are recognized for nephrotic syndromes. Despite in each patient, should be administered at the time of the minimum rate of infusion practicable.

3.1 Use of IVIG to treat infantile botulism

The use of immunoglobulins for the treatment of neonatal botulism is controversial, and the current standard of care is to use the recommended dose of 0.5-1.0 mg/kg for the first 24 hours of life and then to continue at 0.5 mg/kg every 24 hours for a total of 4 days. The rationale for this dosage regimen is based on the findings of a number of studies that have demonstrated that the use of immunoglobulins in neonatal botulism is associated with a reduction in the severity of the disease and an increase in the survival rate of affected infants. However, the optimal dosage regimen for neonatal botulism remains unclear, and further research is needed to determine the most effective and safe approach to the use of immunoglobulins in this setting.

3.2 Administration

• Begin infusion slowly, about 0.5 mL of liquid per minute.

• Monitor vital signs continuously during administration.

• Administer BabyBIG by slow intravenous infusion. A 0.9% sodium chloride injection or normal saline solution at 0.5 mL/kg per hour (20 mL/kg per day) is recommended.

• If necessary, adjust the infusion rate to maintain an adequate blood pressure. If the patient develops a hemodynamic response to the administration of the drug, discontinue the infusion and administer epinephrine.

• As adverse reactions experienced by patients treated with immune globulin intravenous (human) (IGIV) products have been related to the infusion of the drug, if the patient develops a minor side effect (e.g., flushing), slow the rate of infusion or temporarily interrupt the infusion. If anaphylaxis or hypotension develops in blood pressure occur, discontinue the infusion and administer epinephrine.

3.3 Use of IVIG in Neonatal Botulism

The use of intravenous immunoglobulin (IVIG) for the treatment of neonatal botulism is controversial. The current standard of care is to use the recommended dose of 0.5-1.0 mg/kg for the first 24 hours of life and then to continue at 0.5 mg/kg every 24 hours for a total of 4 days. The rationale for this dosage regimen is based on the findings of a number of studies that have demonstrated that the use of IVIG in neonatal botulism is associated with a reduction in the severity of the disease and an increase in the survival rate of affected infants. However, the optimal dosage regimen for neonatal botulism remains unclear, and further research is needed to determine the most effective and safe approach to the use of IVIG in this setting.
7 DRUG INTERACTIONS

- Avoid administration of BiPab with other drugs with known mixed effects. It is recommended that BiPab be administered separately from other drugs or medications that the patient may be receiving (see DOSE AND ADMINISTRATION [2]).

- Administration of BiPab in combination with any other IgE-specific medications that may interfere with the immune response to live virus vaccines such as polo, measles, mumps, and rubella; THE VACCINATION WITH LIVE VIRUS VACCINES SHOULD BE Deferred AT LEAST THREE (3) MONTHS BEFORE ADMINISTRATION of BiPab.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

BiPab has been studied for safety and efficacy only in patients below one year of age (poooLEN/ACTIVITY [2]) and CLINICAL STUDIES [14]. It has not been tested in other populations.

10 OVERDOSAGE

Although limited data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload.11

11 DESCRIPTION

BiPab, Bivalent Botulism Immune Globulin Intravenous (Human) (BiPab), is a solvent-detergent-treated, sterile, lyophilized powder of immunoglobulin (IgG), stabilized with 5% sucrose and 1% albumin (Human). It contains no preservative. The purified immunoglobulin is derived from pooled adult plasma from persons who were immunized with the recombinant botulinum botulinum vaccine for serotypes A and B (RIBV), and were not selected for their high titers of neutralizing antibody against botulinum neurotoxin type A and B. All donors were treated and found to be negative for antibodies against the human immunoglobulin and the Hepatitis B and Hep C viruses.

The pooled plasma was fractionated by cold ethanol precipitation of the proteins according to the Collidine fractionation method, modified by a yeast product suitable for intravenous administration.16,17 Several steps in the manufacturing process have been validated for their ability to kill or remove viruses that may not have been detected in the Source Plasma.18,19,20

These include Collidine/Crystallization Fractionation I through Superamul® Fractionation and Bacterial Inactivations, steps 1 through 2, and the 2% final filter, and solvent/detergent viral inactivation. These virus reduction steps have been validated in a series of in vitro experiments involving exposure of the vaccine to inactivants and/or Human Immunodeficiency Virus type 1 (HIV-1) and the following model viruses: bovine viral diarrhea virus (BVDV) as a model for RNA viruses, mouse monocytotropic virus (MMV) as a model for Hepatitis A virus; and paravaccines (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, as shown in the following table.

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Reduction Mean Log</th>
<th>Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVDV</td>
<td>4.63</td>
<td>&gt;16</td>
</tr>
<tr>
<td>MMV</td>
<td>5.51</td>
<td>&gt;16</td>
</tr>
<tr>
<td>PRV</td>
<td>6.27</td>
<td>&gt;16</td>
</tr>
<tr>
<td>FCV</td>
<td>7.03</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Sindbis Virus</td>
<td>9.02</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

Additional testing performed with bovine parvovirus (as a model for parvovirus B19) showed a mean cumulative reduction factor of greater than 7.34 log, for Collidine/Crystallization Fractionation I through Superamul® Fractionation and Bacterial Inactivations, steps 1 through 2, and the 2% final filter, and solvent/detergent viral inactivation. These virus reduction steps have been validated in a series of in vitro experiments involving exposure of the vaccine to inactivants and/or Human Immunodeficiency Virus type 1 (HIV-1) and the following model viruses: bovine viral diarrhea virus (BVDV) as a model for RNA viruses, mouse monocytotropic virus (MMV) as a model for Hepatitis A virus; and paravaccines (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, as shown in the following table.

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Reduction Mean Log</th>
<th>Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVDV</td>
<td>4.63</td>
<td>&gt;16</td>
</tr>
<tr>
<td>MMV</td>
<td>5.51</td>
<td>&gt;16</td>
</tr>
<tr>
<td>PRV</td>
<td>6.27</td>
<td>&gt;16</td>
</tr>
<tr>
<td>FCV</td>
<td>7.03</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Sindbis Virus</td>
<td>9.02</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

When reconstituted with Sterile Water for Injection (USP), each cubic centimeter (1ml) contains approximately 55 to 100 IgG immunoglobulin, primarily IgG, and trace amounts of IgA and IgM 50 to 100 mg (10 mg albumen), and approximately 240 to 260 mg sodium. The reconstituted solution should appear colorless and transparent (see DOSAGE AND ADMINISTRATION [2]) and PH/TEMPERATURE [5].

12 CLINICAL PHARMACOLOGY

Botulism contains IgG antibodies from the immunized donors who contributed to the plasma pool from which the product was derived. The titer of the antibody in the reconstituted product is approximately 10 million titer units. Each line of botulinum type A is at least 4.0 titer units for type A- and B-identifiable 1.0 of botulinum antibodies neutralized in 10% of the patients, Botulism, green, and botulinum toxin, B.Both the antibody against botulinum neurotoxin C, D, and E have not been determined. In the case of infants with botulinum toxin exposure to botulinum neurotoxin type A or B, this product is expected to provide the relevant antibodies at levels sufficient to neutralize the expected levels of circulating neurotoxin.12,13,14

12.1 Mechanism of Action

Botulism contains antibodies specific for botulinum neurotoxin types A and B that bind to and neutralize the active toxin type A and B in the patient.

12.2 Pharmacokinetics

Formal studies on pharmacokinetics of pharmacokinetics have not been conducted with BiPab.

12.3 Pharmacodynamics

- Studies in non-human primates have been performed. However, the following table summarizes the mean serum titer of the anti-A component of Botulism following administration.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Titers (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>50</td>
</tr>
</tbody>
</table>

The half-life of injected BiPab has been shown to be approximately 20 days in infants. In volunteers, it is in agreement with existing data on other immunoglobulin preparations.15

13 CLINICAL STUDIES

Two clinical trials in infant botulinum were performed. (1) A well-defined and well-controlled study to evaluate the safety and efficacy of Botulism (BiPab) and (2) an open label study to collect additional safety and confirm efficacy of BiPab. In the adequate and well-controlled study, infants were given with the first 3 doses of hospital admission to 59 patients with laboratory-confirmed infant botulism, has been shown to be effective in the treatment of infant botulism. A well-defined and well-controlled study to evaluate the safety and efficacy of Botulism (BiPab) and (2) an open label study to collect additional safety and confirm efficacy of BiPab. In the adequate and well-controlled study, infants were given with the first 3 doses of hospital admission to 59 patients with laboratory-confirmed infant botulism, has been shown to be effective in the treatment of infant botulism.

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

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

The observed reduction in length of hospital stay was statistically significant (p<0.05) with the exception of the 0 to 6 day age stratum, where small patient numbers limited the statistical power of the clinical study. Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

The observed reduction in length of hospital stay was statistically significant (p<0.05) with the exception of the 0 to 6 day age stratum, where small patient numbers limited the statistical power of the clinical study. Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

Length of hospital stay was analyzed in the adequate and well-controlled study by race/ethnicity.

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

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

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

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

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

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

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