

Adverse Event	BabyBIG N=65	Placebo* N=64
	n (%)	
N (%) of Patients with any AE	20 (31)	29 (45)
Rash erythematous	9 (14)	5 (8)
Otitis media	7 (11)	5 (8)
Pneumonia	7 (11)	9 (14)
Anemia	3 (5)	9 (14)
Hyponatremia	3 (5)	9 (14)
Hypertension	1 (2)	3 (5)
Respiratory arrest	1 (2)	6 (9)
Urinary tract infection	1 (2)	8 (13)
Convulsions	0	3 (5)

* Both Gammagard 5% and Gammagard S/D 5% were used as placebo in this study.

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

Adverse Event	BabyBIG N=293 N (%)
Patients with Any AE	285 (97)
Blood pressure increased	221 (75)
Dysphagia	190 (65)
Irritability	121 (41)
Atelectasis	113 (39)
Rhonchi	100 (34)
Pallor	83 (28)
Loose stools	73 (25)
Dermatitis contact	70 (24)
Rash erythematous	64 (22)
Vomiting	58 (20)
Nasal congestion	54 (18)
Edema	54 (18)
Oxygen saturation decreased	51 (17)
Pyrexia	51 (17)
Body temperature decreased	48 (16)
Blood pressure decreased	47 (16)
Cardiac murmur	45 (15)
Cough	39 (13)
Rales	37 (13)
Abdominal distension	33 (11)
Breath sounds decreased	30 (10)
Dehydration	30 (10)
Agitation	29 (10)
Hemoglobin decreased	27 (9)
Stridor	26 (9)
Lower respiratory tract infection	23 (8)
Oral candidiasis	23 (8)
Injection-site reaction	21 (7)
Tachycardia NOS	20 (7)
Peripheral coldness	19 (7)
Dyspnea NOS	16 (6)
Hyponatremia	16 (6)
Injection-site erythema	15 (5)
Intubation NOS	15 (5)
Metabolic acidosis	15 (5)
Neurogenic bladder	15 (5)
Anemia	14 (5)
Tachypnea	14 (5)

Adverse event coding was used in the open label study to distinguish between 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.

6.2 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 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.^[22, 23]

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 overall post-approval use of other IGIV products, as shown in the following table.

<i>Respiratory</i>	Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
<i>Cardiovascular</i>	Cardiac arrest, thromboembolism, vascular collapse, hypotension
<i>Neurological</i>	Coma, loss of consciousness, seizures, tremor
<i>Integumentary</i>	Steven-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
<i>Hematologic</i>	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
<i>General / Body as a Whole</i>	Pyrexia, rigors
<i>Musculoskeletal</i>	Back pain
<i>Gastrointestinal</i>	Hepatic dysfunction, abdominal pain

7 DRUG 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)]*.

- Antibodies present in immune globulin preparations 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 APPROXIMATELY THREE OR MORE MONTHS AFTER ADMINISTRATION OF BabyBIG. If such vaccinations were given shortly before or after BabyBIG administration, revaccination may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.4 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.

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.^[1]

11 DESCRIPTION

BabyBIG, Botulism Immune Globulin Intravenous (Human) (BIG-IV), is a solvent-detergent-treated, sterile, lyophilized powder of immunoglobulin G (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 pentavalent botulinum toxoid and selected for their high titers of neutralizing antibody against botulinum neurotoxins type A and B. All donors were tested and their sera 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/Oncley method, modified to yield a product suitable for intravenous administration.^[24,25] 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.^[1,26-29]

These include Cohn/Oncley fractionation (Fraction I through Supernatant III Filtrate); nanofiltration through one 75-nm and two 35-nm filters; 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 following model viruses: bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; mouse encephalomyelitis virus (MEMV) 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 log₁₀ reductions range from 4.63 to greater than 16 log₁₀ as shown in the following table.

Process Step	Mean Reduction Factor (log ₁₀)					
	Enveloped Viruses (size in nm)					Non-Enveloped Viruses (size in nm)
	Sindbis (60-70)	HIV-1 (80-100)	PRV (120-200)	BVDV (40-60)	MEMV (22-30)	FCV (35-39)
Cohn/Oncley fractionation	6.6	> 9.44	> 10.37	6.25	4.06	Not done
Nanofiltration	≥ 6.84	Not done	Not done	≥ 5.4	Not done	≥ 6.92
Solvent/detergent treatment	Not done	> 4.51	> 5.53	> 4.85	0.57*	Not done
Cumulative Reduction Factor (log₁₀)	≥ 13.44	> 13.95	> 15.9	≥ 16.5	4.63	≥ 6.92

* 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 7.34 log₁₀ for Cohn/Oncley fractionation and solvent/detergent treatment followed by hydrophobic chromatography. A mean cumulative reduction factor of 2.55 log₁₀ was observed for removal of porcine parvovirus by nanofiltration.

When reconstituted with Sterile Water for Injection USP, each cubic centimeter (milliliter) contains approximately 50 ± 10 mg immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg sucrose; 10 mg albumin (human); and approximately 20 x 10⁻³ mEq sodium. The reconstituted solution should appear colorless and translucent *[see DOSAGE AND ADMINISTRATION (2.1), WARNINGS AND PRECAUTIONS (5)]*.

12 CLINICAL PHARMACOLOGY

BabyBIG contains IgG antibodies from the immunized donors who contributed to the plasma pool from which the product was derived. The titer of antibodies in the reconstituted product against type A botulinum toxin is at least 15 IU/mL and against type B toxin is at least 2.0 IU/mL. For toxin types A and B, by definition, 1 IU of botulinum antitoxin neutralizes 10,000 intraperitoneal mouse LD₅₀ of botulinum toxin. The titers of antibody against botulinum neurotoxins C, D, and E have not been determined. In the case of infants who may be exposed 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.^[14, 30]

12.1 Mechanism of Action

BabyBIG contains antibodies specific for botulinum neurotoxin types A and B that bind to and neutralize circulating toxin types A and B in the patient.

12.2 Pharmacodynamics

Formal studies on pharmacodynamics have not been conducted with BabyBIG.

12.3 Pharmacokinetics

Traditional pharmacokinetic studies of BabyBIG have not been performed. However, the following table summarizes the mean serum titer of the anti-A component of BabyBIG following administration.

Time	BabyBIG Lot 1 Anti-A Titer (mean ± S.D.)	BabyBIG Lot 2 Anti-A Titer (mean ± S.D.)
	mIU/mL	
Day 1	Not done	537.1 ± 213.4
Week 2	106.7 ± 44.6	192.2 ± 71.2
Week 4	90.0 ± 39.2	155.5 ± 56.7
Week 8	54.9 ± 22.8	96.0 ± 33.2
Week 12	26.0 ± 20.5	61.4 ± 32.3
Week 16	15.6 ± 10.4	33.0 ± 22.3
Week 20	7.6 ± 6.6	19.3 ± 14.1

NOTE: 1 IU of anti-type A or anti-type B antibody neutralizes, by definition, 10⁴ mouse LD₅₀ of botulinum toxin.

The half-life of injected BabyBIG has been shown to be approximately 28 days in infants,^[14] which is in agreement with existing data for other immunoglobulin preparations.^[2,14]

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) an open label study to collect additional safety data and confirm efficacy (N=293). In the adequate and well-controlled clinical study, BabyBIG, given within the first 3 days of hospital admission to 59 patients with laboratory-confirmed infant botulism, has been shown to reduce the following:

	Average Length in Weeks		p-value
	Placebo* N=63	BabyBIG N=59	
Hospital stay	5.7	2.6	p<0.0001
Intensive Care Unit stay	3.6	1.3	p<0.01
Mechanical ventilation	2.4	0.7	p<0.05
Tube-feeding	10.0	3.6	p<0.01

* Both Gammagard 5% and Gammagard S/D 5% were used as placebo in this study.

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

Age (days)	Mean Length of Hospital Stay in Weeks		
	Placebo* N=63	BabyBIG (RCT) N=59	BabyBIG (OLS) N=206
0-60	3.8 (N=10)	2.8 (N=10)	2.0 (N=46)
61-120	5.6 (N=29)	1.9 (N=17)	2.0 (N=68)
>120	6.6 (N=24)	3.0 (N=32)	1.8 (N=92)

RCT = randomized clinical trial

OLS = open label study

* Both Gammagard 5% and Gammagard S/D 5% were used as placebo in this study.

The observed reduction in length of hospital stay was statistically significant (p<0.01) with the exception of the 0 to 60-day age stratum, where small patient numbers limited the statistical power.

Length of hospital stay was analyzed in the adequate and well-controlled study by race (white versus non-white):

RACE	Mean Length of Hospital Stay in Weeks	
	Placebo*	BabyBIG (RCT)
White	6.3 (N=40)	2.8 (N=35)
Non-white	4.6 (N=23)	2.4 (N=24)

* Both Gammagard 5% and Gammagard S/D 5% were used as placebo in this study.

Length of hospital stay was significantly reduced in both white and non-white patients (p=0.002).

BabyBIG has not been tested for safety and efficacy in adults.

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16 HOW SUPPLIED/STORAGE AND HANDLING

- NDC 68403-1100-6, 100 mg ± 20 mg lyophilized immunoglobulin single-dose vial individually packaged in a carton, supplied with 2 mL Sterile Water for Injection USP for reconstitution.
- Store the vial containing the lyophilized product between 2° and 8°C (35.6° to 46.4°F). Do not store BabyBIG in the reconstituted state.
- Use reconstituted BabyBIG within 2 hours.
- Do not use beyond expiration date, and dispose unused product in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

- Discuss the risks and benefits of BabyBIG use with the patient’s legal guardians, including the possibility of adverse reactions, e.g., hypersensitivity reactions such as anaphylaxis, as well as aseptic meningitis, TRALI, hemolysis, renal failure, and thrombosis *[see WARNINGS AND PRECAUTIONS (5)]*.
- Inform patient’s legal guardians that BabyBIG is made from human plasma and may contain infectious agents that can cause disease. While the risk of transmitting an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, the patient’s guardian should report any symptoms that concern them *[see WARNINGS AND PRECAUTIONS (5.3)]*.
- Inform patient’s legal guardians that BabyBIG may interfere with immune response to live viral vaccines (e.g., MMR) and instruct them to notify the healthcare provider of this potential interaction when the patient is to receive vaccinations *[see DRUG INTERACTIONS (7)]*.

For additional information concerning BabyBIG, contact:

Infant Botulism Treatment and Prevention Program
California Department of Public Health
850 Marina Bay Parkway, Room E-361
Richmond, California 94804
Telephone: 510-231-7600
US Govt. License No. 1797

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