BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV)
California Department of Health Services

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 immunized with pentavalent botulinum toxoid who were selected for their high titers of neutralizing antibody against botulinum neurotoxins type A and B. All donors were tested and found 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[1,2]. 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[3-7]. 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 $\log_{10}$ reductions range from 6.07 to greater than 16 $\log_{10}$ as shown in the following table.

	Mean Reduction Factor ($\log_{10}$)					
	Enveloped Viruses (size in nm)				**Non-Enveloped Viruses (size in nm)**	
Process Step	**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 ($\log_{10}$)	≥ 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 $\log_{10}$ for Cohn/Oncley 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 (milliliter) contains approximately 50 ± 10 mg immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg sucrose; 10 mg albumin (human); and 20 x 10^{-3} mEq sodium. The reconstituted solution should appear colorless and translucent.

Two lots of BabyBIG have been manufactured: BabyBIG Lot 1 was used in the controlled clinical trial as well

as in the open label study, and BabyBIG Lot 2 was used only in the open label study (see Clinical Studies section).

CLINICAL PHARMACOLOGY

BabyBIG contains IgG antibodies representative of 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 4 IU/mL. For toxin types A and B, by definition, 1 IU of botulinum antitoxin neutralizes 10,000 intraperitoneal mouse LD_{50} 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 toxin types A or B, this product is expected to provide the relevant antibodies at levels sufficient to neutralize the expected levels of circulating neurotoxin[8]. 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

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 [9,10]; thus, a single intravenous infusion of BabyBIG is expected to provide a protective level (more than 0.1 mIU/mL) of neutralizing antibodies for 6 months.

INDICATIONS AND USAGE

BabyBIG is indicated for the treatment of patients below one year of age with infant botulism caused by toxin type A or B.

Clinical Studies - Infant Botulism

Two clinical studies of BabyBIG 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:

(a) the average length of hospital stay, from 5.7 weeks (placebo group) to 2.6 weeks (BabyBIG –treated group; $p<0.0001$);

(b) the average length of stay in the hospital's Intensive Care Unit, from 3.6 weeks (placebo) to 1.3 weeks (BabyBIG; $p<0.01$);
(c) the average length of time on a mechanical ventilator, from 2.4 weeks (placebo) to 0.7 weeks (BabyBIG; $p<0.05$); and (d) the average number of weeks the patients had to be tube-fed, from 10.0 weeks (placebo) to 3.6 weeks (BabyBIG; $p<0.01$).
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	BabyBIG (AWC)	BabyBIG (OLS)
0-60	3.8	2.8	2.0
61-120	5.6	1.9	2.0
>120	6.6	3.0	1.8

AWC= adequate and well-controlled
OLS = open-label 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
White	6.3	2.8
Non-white	4.6	2.4

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.

CONTRAINDICATIONS

As with other immunoglobulin preparations, BabyBIG should not be used in individuals with a prior history of severe reaction to other human immunoglobulin preparations [7,9-11]. Individuals with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to the subsequent administration of blood products that contain immunoglobulin A. BabyBIG contains only trace amounts of immunoglobulin A.

WARNINGS

Immune globulin intravenous (human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death[12,13]. While these reports of renal dysfunction and acute renal failure have been associated with the use of many licensed IGIV products, those that contained sucrose as a stabilizer and were administered at daily doses of 400 mg/kg or greater have accounted for a disproportionate share of the total number[14]. BabyBIG contains sucrose as a stabilizer. Patients predisposed to acute renal failure include those patients with any degree of pre-existing renal insufficiency, diabetes mellitus, volume depletion, sepsis, paraproteinemia, or who are receiving known nephrotoxic drugs. Especially in such patients, BabyBIG should be administered at the minimum concentration available and at the minimum rate of

infusion practicable[7].

BabyBIG is made from human plasma and, like other plasma products, carries the possibility for transmission of blood-borne viral agents and, theoretically, the Creutzfeldt-Jakob disease agent. The risk of transmission of recognized blood-borne viruses has been reduced by screening plasma donors for prior exposure to certain viruses and for the current presence of certain viral infections (DESCRIPTION section), and by the viral inactivation and/or removal properties of the precipitation procedures used for the purification of BabyBIG. Despite these measures, some as yet unrecognized blood-borne viruses may not be inactivated by the manufacturing process; therefore, BabyBIG, like any other blood product, should be given only if a benefit is expected. The patient's legal guardian should discuss the risks and benefits of this product with the attending physician.

Epinephrine should be available for the treatment of an acute anaphylactic reaction (PRECAUTIONS section).

PRECAUTIONS

General

BabyBIG should only be administered as an intravenous infusion, since other routes of administration have not been evaluated. BabyBIG should not be used if the reconstituted solution is turbid.

During administration, the patient's vital signs should be monitored continuously and the patient should be carefully observed for any associated symptoms. Although acute systemic allergic reactions were not seen in clinical trials with BabyBIG (ADVERSE REACTIONS section), epinephrine should be available for treatment of acute allergic symptoms. If hypotension or anaphylaxis occurs, the administration of BabyBIG should be discontinued immediately and supportive care given as needed.

BabyBIG does not contain a preservative. After reconstitution of the lyophilized product, the vial should be entered only once for the purpose of administration, and the infusion should begin within 2 hours. No patients should be volume-depleted prior to the initiation of the BabyBIG infusion. Renal function, including the measurement of blood urea nitrogen or serum creatinine, should be also assessed prior to the initial infusion of BabyBIG. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential risk for developing acute renal failure [7,9-11]. Do not exceed the recommended infusion rate of 1 mL/kg/hour (50 mg/kg/hr), and follow the infusion schedule closely (INFUSION section).

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV administration[15-18]. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including the following: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominately from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination to rule out other causes of meningitis [15-18]. AMS may occur more frequently in association with high total doses (2 g/kg) of IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae[7].

Drug Interactions

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 FIVE MONTHS AFTER ADMINISTRATION OF BabyBIG. If such vaccinations were given shortly before or after BabyBIG administration, a revaccination may be necessary. 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 ADMINISTRATION section.)

Pediatrics and Geriatrics

BabyBIG has been tested for safety and efficacy only in patients less than one year of age. BabyBIG has not been tested for safety or efficacy in other pediatric, adult, or geriatric populations.

Pregnancy

Animal reproduction studies have not been conducted with BabyBIG; therefore it is not known whether BabyBIG can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

ADVERSE REACTIONS

Different methodologies were used to collect adverse events in the controlled study and open label study. Minor clinical events that were not recorded as adverse events in the controlled study were recorded as adverse events in the open label study. As a result, a larger number of adverse events were recorded in the open label study. The only adverse event possibly related to BabyBIG administration was a mild, transient erythematous rash of the face or trunk. The following table summarizes the occurrence of rash by day of study relative to day of treatment.

Day of Study Relative to Treatment Day		RCT		OLS
		Placebo (N=64)	BabyBIG (N=65)	BabyBIG (N=293)
		n (%)		
Day -5		0 (0)	1 (2)	6 (2)
Day -4		2 (3)	1 (2)	5 (2)
Day -3		3 (5)	4 (6)	6 (2)
Day -2		5 (8)	2 (3)	22 (8)
Day -1		4 (6)	11 (17)	28 (10)
Day 0*	Before†	5 (8)	9 (14)	32 (11)
	During & After†	2 (3)	9 (14)	39 (13)
Day +1		2 (3)	1 (2)	18 (6)
Day +2		1 (2)	2 (3)	13 (4)
Day +3		3 (5)	0 (0)	7 (2)
Day +4		1 (2)	2 (3)	11 (4)
Day +5		2 (3)	0 (0)	5 (2)

* Day 0 is the day of treatment
† In reference to treatment

When only treatment emergent events are considered, 14% of the BabyBIG-treated patients experienced erythematous rash during or after study infusion in the controlled study. Eight percent of placebo-treated patients also experienced erythematous rash in the controlled study. A similar rash is known to occur both in infant botulism patients who have not received any IGIV products[19] and in patients treated with other IGIVs[9,10], making it difficult to ascertain the causality of the rash.

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

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)

In the open label study, 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.

Many of the adverse events observed in the controlled and open label studies are part of the known pathophysiology of infant botulism [19, 23-26]. Minor reactions such as chills, muscle cramps, back pain, fever, nausea, vomiting, and wheezing were the most frequent adverse reactions observed during the clinical trials of other, similarly-prepared human IGIVs [20]. The incidence of these reactions was less than 5.0% of all infusions, and they were most often related to infusion rates [14]. If a patient develops a minor side effect, slow the rate of infusion immediately or temporarily interrupt the infusion.

Severe reactions, such as angioneurotic edema and anaphylactic shock, although not observed during clinical trials with BabyBIG, are a possibility [21,22]. Clinical anaphylaxis may occur even when the patient is not known to be sensitive to immune globulin products. A reaction may be related to the rate of infusion; therefore, carefully adhere to the infusion rates as outlined under "DOSAGE AND ADMINISTRATION." If anaphylaxis or a drop in blood pressure occurs, discontinue the infusion and administer epinephrine [7,9-11].

Increases in serum creatinine and BUN have been observed as soon as one to two days following treatment with other IGIVs. Other severe renal adverse events that have been seen following IGIV therapy include acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and osmotic nephrosis [12-14,20].

OVERDOSAGE

Although limited data are available, clinical experience with other immunoglobulin preparations suggests that the major manifestations would be those related to volume overload [7].

DOSAGE AND ADMINISTRATION

The recommended total dosage of BabyBIG is 1 mL/kg (50 mg/kg), given as a single intravenous infusion as soon as the clinical diagnosis of infant botulism is made. BabyBIG should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to, those with diabetes mellitus, volume depletion, paraproteinemia, sepsis, or who are receiving known nephrotoxic drugs). In the absence of prospective data allowing identification of the maximum safe dose, concentration, and rate of infusion in these patients, do not exceed the dose, concentration, and rate of infusion recommended below.

Preparation for Administration:

Remove the tab portion of the vial cap and clean the rubber stopper with 70% alcohol or equivalent. Reconstitute the lyophilized powder with 2 mL of Sterile Water for Injection USP, to obtain a 50 mg/mL BabyBIG 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 water. The lyophilized powder is supplied in an evacuated vial; therefore, the water should transfer by suction (the jet of water should be aimed to the side of the vial). After the water is transferred into the evacuated vial, the residual vacuum should be released to hasten the dissolution.

Rotate the container gently to wet all the powder. An approximately 30-minute interval should be allowed for dissolving the powder. DO NOT SHAKE THE VIAL, AS THIS WILL CAUSE FOAMING.

BabyBIG should be inspected visually for particulate matter and discoloration prior to administration. Infuse

the solution only if it is colorless, free of particulate matter, and not turbid.

Infusion: Infusion should begin within 2 hours after reconstitution is complete and should be concluded within 4 hours of reconstitution. Vital signs should be monitored continuously during infusion. BabyBIG should be administered intravenously using low volume tubing and a constant infusion pump (*i.e.*, an IVAC pump or equivalent). Pre-dilution of BabyBIG before infusion is not recommended. The product should be administered through a separate intravenous line. If this is not possible, it may be "piggybacked" into a pre-existing line if that line contains either Sodium Chloride Injection USP, or one of the following dextrose solutions (with or without NaCl added): 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, or 20% dextrose in water. If a pre-existing line must be used, BabyBIG should not be diluted more than 1:2 with any of the above-named solutions. Admixtures of BabyBIG with any other solutions have not been evaluated. Use of an in-line or syringe-tip sterile, disposable filter (18 μm) is recommended for the administration of BabyBIG.

Infusion Rate: The infusion should begin slowly. BabyBIG should be administered intravenously at 0.5 cc per kg body weight per hr (25 mg/kg/hr). If no untoward reactions occur after 15 minutes, the rate may be increased to 1.0 cc/kg/hr (50 mg/kg/hr, see table below). DO NOT EXCEED THIS RATE OF ADMINISTRATION. The patient should be monitored closely during and after each rate change. At the recommended rates, infusion of the indicated dose should take 67.5 minutes total elapsed time.

Time	Rate of 5% Solution	mg/kg/hr
0–15 min	0.5 cc/kg/hr	25
15 min to end of infusion	1.0 cc/kg/hr	50

Minor adverse reactions experienced by patients treated with IGIV products have been related to the infusion rate. If the patient develops a minor side effect (*i.e.*, flushing), slow the rate of infusion or temporarily interrupt the infusion. If anaphylaxis or a significant drop in blood pressure occurs, discontinue the infusion and administer epinephrine.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. The syringes and needles should never be reused.

HOW SUPPLIED

BabyBIG is supplied in a single dose vial containing approximately 100 mg ± 20 mg lyophilized immunoglobulin for reconstitution with 2 mL Sterile Water for Injection USP.

STORAGE

The product should be stored between 2^{o} and 8^{o}C (35.6^{o} to 46.4^{o}F). Reconstituted BabyBIG should be used

within 2 hours. BabyBIG should not be stored in the reconstituted state.

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For additional information concerning BabyBIG®, contact:

Infant Botulism Treatment and Prevention Program
California Department of Health Services
850 Marina Bay Parkway, Room E-361
Richmond, California 94804
Telephone: 510-231-7600
US Govt. License No. 1622

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