



Prescription and Patient Enrollment Form

- I WANT TO: Accept as prescription (**All sections**)
 Perform insurance benefits verification (not needed if home care is selected) (**Sections B and C**)
 Enroll my patient in the GARDian program (**Section B**)*

**SECTION A
PHYSICIAN
INFORMATION
(REQUIRED)**

Physician name	Office contact
Address	City / State / ZIP
Telephone	Fax
DEA #	E-mail
State license #	NPI

**SECTION B
PATIENT
INFORMATION**

Patient name	Date of birth
Address	City / State / ZIP
Telephone	ICD-9 Code

**SECTION C
INSURANCE
INFORMATION**

Insurance company	Telephone
Insured's name	Relationship to patient
Policy/Group #	Identification #
Prescription card attached?	<input type="checkbox"/> Yes <input type="checkbox"/> No

PRESCRIPTION DOSING

For patients with primary immunodeficiency, monthly doses of approximately 300 to 600 mg/kg infused at 3- to 4-week intervals are commonly used.¹

<input type="checkbox"/> GAMMAGARD LIQUID [Immune Globulin Intravenous (Human)] 10%	Patient weight	Ordered dose
<input type="checkbox"/> GAMMAGARD S/D [Immune Globulin Intravenous (Human)]	Frequency	Refills (months)
<input type="checkbox"/> GAMMAGARD S/D [Immune Globulin Intravenous (Human)], IgA less than 1 µg/mL in a 5% solution		

SPECIAL INSTRUCTIONS

Infusion center Hospital Physician office Home care/Specialty pharmacy _____

Premedication _____

Other _____

Notify me with periodic updates.
 I verify that the patient has been informed about his/her diagnosis and treatment.
 I verify that the patient has or will have his/her own copy of the GARDian program materials (optional).

Physician signature (required) _____ Date _____

DISPENSE AS WRITTEN

I verify that the patient and prescriber information contained in this enrollment form is complete and accurate to the best of my knowledge and that I have prescribed GAMMAGARD based on my professional judgment of medical necessity. I authorize Parexel or its affiliated companies or subcontractors to forward this prescription electronically, by facsimile, or by mail to a dispensing pharmacy chosen by the above-named patient. I also authorize Parexel to perform any steps necessary to obtain reimbursement for GAMMAGARD, including but not limited to insurance verification and case assessment. I understand that Parexel may need additional information, and I agree to provide it as needed for the purposes of reimbursement. I certify that I have obtained the patient's consent to release this information for the patient's enrollment in the GARDian program.

For more information, call 1-877-655-GARD (4273) or visit www.myGARDian.com.

*The GARDian program is designed to facilitate the compliance of HIPAA as well as other privacy laws.

[Immune Globulin Intravenous (Human)] 10%

GAMMAGARD LIQUID is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. These include but are not limited to congenital X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Important Risk Information for GAMMAGARD LIQUID

GAMMAGARD LIQUID is contraindicated in patients with known anaphylactic or severe hypersensitivity responses to Immune Globulin (Human). Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

Glycine, an amino acid, is used as a stabilizer. GAMMAGARD LIQUID does not contain sucrose.

GAMMAGARD LIQUID is made from human plasma. It may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Components used in the packaging of this product are latex-free.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders, and prolonged periods of immobilization.

IGIV products can contain blood group antibodies that may cause a positive direct antiglobulin reaction and, rarely, hemolysis.

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Various mild and moderate reactions, such as headache, fever, fatigue, chills, flushing, dizziness, urticaria, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, muscle cramps, and changes in blood pressure may occur with infusions of Immune Globulin Intravenous (Human).

Please review the accompanying GAMMAGARD LIQUID Prescribing Information for full prescribing details.

The GARDian program is subject to change at any time.

Reference: 1. GAMMAGARD LIQUID [Immune Globulin Intravenous (Human)] 10% [package insert]. Westlake Village, CA: Baxter Healthcare Corporation; October 2009.

GAMMAGARD S/D [Immune Globulin Intravenous (Human)], IgA less than 1 µg/mL in a 5% solution

GAMMAGARD S/D is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. These include but are not limited to congenital X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

GAMMAGARD S/D must not be used in patients with selective IgA deficiency (IgA < 0.05 g/L) where the IgA deficiency is the only abnormality of concern.

Important Risk Information for GAMMAGARD S/D, IgA less than 1 µg/mL in a 5% solution

Patients may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of GAMMAGARD S/D.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

GAMMAGARD S/D does not contain sucrose.

GAMMAGARD S/D, IgA < 1 µg/mL, has a lower IgA concentration than GAMMAGARD S/D which has a concentration of 1 to 2.2 µg/mL. IGIV preparations depleted of IgA (0.4 to 2.9 µg/mL) were shown to be better tolerated by a limited number of patients who reacted to IGIV preparations with higher IgA concentrations. However, the concentration of IgA that will not provoke a reaction is not known, and therefore all IGIV preparations carry the risk of inducing an anaphylactic reaction to IgA. In such instances, a risk of anaphylaxis may exist despite the fact that GAMMAGARD S/D, IgA < 1 µg/mL, contains trace amounts of IgA.

GAMMAGARD S/D is made from human plasma. It may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Certain components used in the packaging of GAMMAGARD S/D contain natural rubber latex.

IGIV products can contain blood group antibodies that may cause a positive direct antiglobulin reaction and, rarely, hemolysis.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders, and prolonged periods of immobilization.

Various minor reactions, such as mild to moderate hypotension, headache, fatigue, chills, backache, leg cramps, lightheadedness, fever, urticaria, flushing, slight elevation of blood pressure, nausea and vomiting may occasionally occur.

Please review the accompanying GAMMAGARD S/D, IgA less than 1 µg/mL in a 5% solution Prescribing Information for full prescribing details.

GAMMAGARD S/D [Immune Globulin Intravenous (Human)]

GAMMAGARD S/D is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. These include but are not limited to congenital X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

GAMMAGARD S/D must not be used in patients with selective IgA deficiency (IgA < 0.05 g/L) where the IgA deficiency is the only abnormality of concern.

Important Risk Information for GAMMAGARD S/D

Patients may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of GAMMAGARD S/D.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

GAMMAGARD S/D does not contain sucrose.

GAMMAGARD S/D is made from human plasma. It may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Certain components used in the packaging of GAMMAGARD S/D contain natural rubber latex.

IGIV products can contain blood group antibodies that may cause a positive direct antiglobulin reaction and, rarely, hemolysis.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders, and prolonged periods of immobilization.

Various minor reactions, such as mild to moderate hypotension, headache, fatigue, chills, backache, leg cramps, lightheadedness, fever, urticaria, flushing, slight elevation of blood pressure, nausea and vomiting, may occasionally occur.

Please review the accompanying GAMMAGARD S/D Prescribing Information for full prescribing details.

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August 2010 HYL3514F 080081

GAMMAGARD LIQUID [Immune Globulin Intravenous (Human)] 10%

DESCRIPTION

GAMMAGARD LIQUID Immune Globulin Intravenous (Human), 10% is a ready-for-use sterile, liquid preparation of highly purified and concentrated immunoglobulin G (IgG) antibodies. The distribution of the IgG subclasses is similar to that of normal plasma.^{1,2} The Fc and Fab functions are maintained in GAMMAGARD LIQUID. Pre-kallikrein activator activity is not detectable. GAMMAGARD LIQUID contains 100 mg/mL protein. At least 98% of the protein is gammaglobulin, the average immunoglobulin A (IgA) concentration is 37 µg/mL, and immunoglobulin M is present in trace amounts. GAMMAGARD LIQUID contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent, and there are no added sugars, sodium or preservatives. The pH is 4.6 to 5.1. The osmolality is 240-300 mOsmol/kg, which is similar to physiological osmolality (285 to 295 mOsmol/kg).³

GAMMAGARD LIQUID is manufactured from large pools of human plasma. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of GAMMAGARD LIQUID is collected only at FDA approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini-pools of the plasma are tested for the presence of HIV-1 and HCV by FDA licensed Nucleic Acid Testing (NAT) and found negative. IgGs are purified from plasma pools using a modified Cohn-Oncley cold ethanol fractionation process, as well as cation and anion exchange chromatography.

To further improve the margin of safety, three dedicated, independent and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent (S/D) treatment,^{4,5} 35 nm nanofiltration,^{6,7} and a low pH incubation at elevated temperature.^{8,9} The S/D process includes treatment with an organic mixture of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80 at 18°C to 25°C for a minimum of 60 minutes.

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed under extreme conditions (e.g., at minimum S/D concentrations, incubation time and temperature for the S/D treatment). Virus clearance studies for GAMMAGARD LIQUID performed in accordance with good laboratory practices (Table 1) have demonstrated that:

- S/D treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes.
- 35 nm nanofiltration removes lipid-enveloped viruses to below detection limits and reduces the non-lipid enveloped viruses HAV and B19V. As determined by a polymerase chain reaction assay, nanofiltration reduced B19V by a mean log₁₀ reduction factor of 4.8 genome equivalents.
- Treatment with low pH at elevated temperature of 30°C to 32°C inactivates lipid-enveloped viruses and encephalomyocarditis virus (EMCV, model for HAV) to below detection limits, and reduces mice minute virus (MMV, model for B19V).

Virus type Family	Enveloped RNA			Enveloped DNA	Non-enveloped RNA		Non-enveloped DNA
	Retroviridae		Flaviviridae	Herpesviridae	Picornaviridae	Parvoviridae	
	HIV-1	BVDV	WNV	PRV	HAV	EMCV	MMV
SD treatment	>4.5	>6.2	n.a.	>4.8	n.d.	n.d.	n.d.
35 nm nanofiltration	>4.5	>5.1	>6.2	>5.6	5.7	1.4	2.0
Low pH treatment	>5.8	>5.5	>6.0	>6.5	n.d. ^b	>6.3	3.1
Overall log reduction factor (ORF)	>14.8	>16.8	>12.2	>16.9	5.7^b	>7.7	5.1

Abbreviations: HIV-1, Human Immunodeficiency Virus Type 1; BVDV, Bovine Viral Diarrhea Virus (model for Hepatitis C Virus and other lipid enveloped RNA viruses); WNV, West Nile Virus; PRV, Pseudorabies Virus (model for lipid enveloped DNA viruses, including Hepatitis B Virus); EMCV, Encephalomyocarditis Virus (model for non-lipid enveloped RNA viruses, including Hepatitis A virus [HAV]); MMV, Mice Minute Virus (model for non-lipid enveloped DNA viruses, including B19 virus [B19V]); n.d. (not done), n.a. (not applicable).

^a For the calculation of these RF data from virus clearance study reports, applicable manufacturing conditions were used. Log₁₀ RFs on the order of 4 or more are considered effective for virus clearance in accordance with the Committee for Medicinal Products for Human Use (CHMP, formerly CPMP) guidelines.

^b No RF obtained due to immediate neutralization of HAV by the anti-HAV antibodies present in the product.

CLINICAL PHARMACOLOGY

Clinical Efficacy

Use of GAMMAGARD LIQUID in patients with Primary Immunodeficiency is supported by the Phase 3 clinical study of subjects who were treated with 300 to 600 mg/kg every 21 to 28 days for 12 months. The 61 subjects in this study were between 6 to 72 years of age, 54% female and 46% male, and 93% Caucasian, 5% African-American, and 2% Asian. Three subjects were excluded from the per-protocol analysis due to non-study product related reasons. The primary efficacy endpoint was the annualized rate of specified acute serious bacterial infections, i.e., the mean number of specified acute serious bacterial infections per subject per year (see Table 2).

	Number of Events
Validated Infections ^a	
Bacteremia / Sepsis	0
Bacterial Meningitis	0
Osteomyelitis / Septic Arthritis	0
Bacterial Pneumonia	0
Visceral Abscess	0
Total	0
Hospitalizations Secondary to Infection	0
Mean Number of Validated Infections per Subject per Year	0
p-value ^b	p < 0.0001
95% Confidence Interval ^b	(0.000, 0.064)

^a Serious acute bacterial infections were defined by FDA and met specific diagnostic requirements.

^b The rate of validated infections was compared with a rate of 1 per subject per year, in accordance with recommendations by the FDA Blood Products Advisory Committee.¹⁰

The secondary efficacy endpoints in this study were the annualized rate of other specified validated bacterial infections (see Table 3), and the number of hospitalizations secondary to all validated infectious complications (see Table 2 and Table 3).

	Number of Events
Validated Infections ^a	
Urinary Tract Infection	1
Gastroenteritis	1
Lower Respiratory Tract Infection: Tracheobronchitis, Bronchiolitis Without Evidence of Pneumonia	0
Lower Respiratory Tract Infection: Other Infections (e.g., Lung Abscess, Empyema)	0
Otitis Media	2
Total	4
Hospitalizations Secondary to Infection	0
Mean Number of Validated Infections per Subject per Year	0.07
95% Confidence Interval	(0.018, 0.168)

^a Other bacterial infections that met specific diagnostic requirements.

In this study, there were no validated acute serious bacterial infections in any of the treated subjects. The annualized rate of acute serious bacterial infections was significantly less than (p < 0.0001) the rate of one infection per year, in accordance with recommendations by the FDA Blood Products Advisory Committee.¹⁰ Four of the 61 subjects reported a total of 4 other specified validated bacterial infections. None were serious or severe, none resulted in hospitalization, and all resolved completely.

The rate of all clinically-defined but non-validated infections was 3.4 infections per patient per year. These consisted primarily of recurrent episodes of commonly observed infections in this patient population - sinusitis, bronchitis, nasopharyngitis, urinary tract infections, and upper respiratory infections.

Pharmacokinetics

The overall pharmacokinetic characteristics of Immune Globulin Intravenous (Human) [IGIV] products are well-described in the literature.^{11,12} Following infusion, IGIV products show a biphasic decay curve. The initial (α) phase is characterized by an immediate post-infusion peak in serum IgG and is followed by rapid decay due to equilibration between the plasma and extravascular fluid compartments. The second (β) phase is characterized by a slower and constant rate of decay.

The commonly cited "normal" half life of 18 to 25 days is based on studies in which tiny quantities of radiolabeled IgG are injected into healthy individuals.^{13,14} When radiolabeled IgG was injected into patients with hypogammaglobulinemia or agammaglobulinemia, highly variable half-lives ranging from 12 to 40 days were observed.^{13,14} In other radiolabeled studies, high serum concentrations of IgG, and hypermetabolism associated with fever and infection, have been seen to coincide with a shortened half-life of IgG.^{14,15,16,17}

In contrast, however, pharmacokinetic studies in immunodeficient patients are based on the decline of IgG concentrations following infusions of large quantities of gammaglobulin. In such trials, investigators have reported uniformly prolonged half-lives of 26 to 35 days.^{16,18,19,20,21,22}

Pharmacokinetic parameters for GAMMAGARD LIQUID were determined from total IgG levels following the fourth infusion. A total of 61 subjects were enrolled and treated. Of these, 57 had sufficient pharmacokinetic data to be included in the dataset. Pharmacokinetic parameters are presented in Table 4.

Parameter	Median	95% Confidence Interval
Elimination Half-Life (T _{1/2} days)	35	(31, 42)
AUC _{0-24h} (mg·days/dL)	29139	(27494, 30490)
C _{max} (Peak, mg/dL)	2050	(1980, 2200)
C _{min} (Trough, mg/dL)	1030	(939, 1110)
Incremental recovery (mg/dL)/(mg/kg)	2.3	(2.2, 2.6)

Abbreviations: AUC= area under the curve;

C_{max}=maximum concentration; C_{min}= minimum concentration

Median IgG trough levels were maintained between 960-1120 mg/dL. These dosing regimens maintained serum trough IgG levels considerably above 450 mg/dL, which is consistent with levels considered to be effective in the treatment of patients with Primary Immunodeficiency.^{23,24} The elimination half-life of GAMMAGARD LIQUID of 35 days was similar to the half-lives reported for other IGIV products.^{13,14,15,17,25,26}

INDICATIONS AND USAGE

Primary Immunodeficiency

GAMMAGARD LIQUID is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. These include but are not limited to congenital X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.^{15,22}

CONTRAINDICATIONS

GAMMAGARD LIQUID is contraindicated in patients with known anaphylactic or severe hypersensitivity responses to Immune Globulin (Human).

Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using GAMMAGARD LIQUID even though it contains low amounts of IgA (average concentration of 37µg/mL). These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immune globulin is clearly indicated. Such patients should only receive intravenous immune globulin with utmost caution and in a setting where supportive care is available for treating life-threatening reactions.

WARNINGS

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.²⁷ Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

Glycine, an amino acid, is used as a stabilizer. GAMMAGARD LIQUID does not contain sucrose.

See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Immune Globulin Intravenous (Human), 10% is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses (see DESCRIPTION). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, at 1-800-423-2862 (in the U.S.). The physician should discuss the risks and benefits of this product with the patient.

GAMMAGARD LIQUID should only be administered intravenously. Other routes of administration have not been evaluated.

Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reactions.

PRECAUTIONS

General

Some viruses, such as B19V (formerly known as Parvovirus B19) or Hepatitis A, are particularly difficult to remove or inactivate. B19V most seriously affects pregnant women, or immune-compromised individuals. Symptoms of B19V infection include fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Evidence of Hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

Components used in the packaging of this product are latex-free.

Renal Function

Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assure that patients are not volume depleted prior to the initiation of infusion of GAMMAGARD LIQUID. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of IGIV products and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk of developing renal dysfunction, it may be prudent to reduce the rate of infusion to less than 3.3 mg IgG/kg/min (< 2 mL/kg/hr).

Hemolysis

IGIV products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.^{28,29,30} Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced red blood cells (RBC) sequestration (see ADVERSE REACTIONS).³¹ IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see PRECAUTIONS: Laboratory Tests).

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema (Transfusion-Related Acute Lung Injury [TRALI]) in patients administered IGIV.³² TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever, and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see PRECAUTIONS: Laboratory Tests).

Thrombotic Events

Thrombotic events have been reported in association with IGIV (see ADVERSE REACTIONS).^{33,34,35,36,37,38,39,40,41} Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders and prolonged periods of immobilization. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see PRECAUTIONS: Laboratory Tests).

Aseptic Meningitis Syndrome

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

Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done [see PRECAUTIONS].

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [see PRECAUTIONS].

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [see PRECAUTIONS].

Information For Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

Drug Interactions

See DOSAGE AND ADMINISTRATION section.

Pregnancy Category C

Animal reproduction studies have not been conducted with GAMMAGARD LIQUID. It is also not known whether GAMMAGARD LIQUID can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMMAGARD LIQUID should be given to a pregnant woman only if clearly indicated. Maternally administered IGIV products have been shown to cross the placenta, increasingly after 30 weeks gestation.^{42,43,44}

Use in Pediatrics

The safety and efficacy of GAMMAGARD LIQUID has not been evaluated in neonates or infants.

ADVERSE REACTIONS

General

Various mild and moderate reactions, such as headache, fever, fatigue, chills, flushing, dizziness, urticaria, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, muscle cramps, and changes in blood pressure may occur with infusions of Immune Globulin Intravenous (Human). In general, reported adverse reactions to GAMMAGARD LIQUID in patients with Primary Immunodeficiency are similar in kind and frequency to those observed with other IGIV products. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. Although hypersensitivity reactions have not been reported in the clinical studies with GAMMAGARD LIQUID immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactic reactions (see WARNINGS).

Clinical Study

Adverse experiences were examined among a total of 61 enrolled subjects with Primary Immunodeficiency who received at least one infusion of GAMMAGARD LIQUID during the Phase 3 multicenter clinical study. For this study, temporally associated adverse events are defined by the FDA as those occurring during or within 72 hours of completion of an infusion. Adverse drug reactions (ADR's) are those adverse events that were deemed by the investigators as causally related to the infusion of GAMMAGARD LIQUID.

Of all adverse experiences, 15 events in 8 subjects were serious. Two serious events, two episodes of aseptic meningitis in one patient, were deemed to be possibly related to the infusion of GAMMAGARD LIQUID.

Among the 896 non-serious adverse experiences, 258 were judged by the investigator to be possibly or probably related to the infusion of GAMMAGARD LIQUID. Of these, 136 were mild, 106 were moderate, and 16 were severe. All of the severe non-serious adverse experiences were transient, did not lead to hospitalization, and resolved without complication. One subject withdrew from the study due to a non-serious adverse experience (papular rash).

Of the 345 temporally related adverse experiences, those occurring in > 5% of subjects are shown in Table 5. Of these events, only headache occurred in association with more than 5% of infusions. All events were expected based on past experiences with intravenous gammaglobulin products.

Event	By Infusion		By Subject	
	Number	Percentage	Number	Percentage
Headache	57	6.90	22	36.1
Fever	19	2.30	13	21.3
Fatigue	18	2.18	10	16.4
Vomiting	10	1.21	9	14.8
Chills	14	1.69	8	13.1
Infusion site events	8	0.97	8	13.1
Nausea	9	1.09	6	9.8
Dizziness	7	0.85	6	9.8
Pain in Extremity	7	0.85	5	8.2
Diarrhea	7	0.85	5	8.2
Cough	5	0.61	5	8.2
Pruritus	5	0.61	4	6.5
Pharyngeal Pain	5	0.61	4	6.5

* Excluding Infections

The majority (227/258) of the non-serious adverse experiences deemed related to study product were considered expected based on previous experience with IGIV products and 31 were considered unexpected. In virtually every case, these unexpected events were either consistent with the subject's specific type of immunodeficiency or with the subject's medical history prior to entering the study. A total of 14 hospitalizations occurred during the study but none were related to infection.

Hematology and clinical chemistry parameters were monitored in all subjects prior to each infusion throughout the 12-month period of study. Mean values for all laboratory parameters remained consistent throughout the study period. Three of the hematology values in one subject were outside of the normal range and reported as non-serious adverse experiences that resolved completely. These were a red cell count of $3.9 \times 10^9/\mu\text{L}$, hematocrit of 31%, and white cell count of $3.88 \times 10^3/\mu\text{L}$. All spontaneously returned to baseline. One subject had an elevated BUN (45 mg/dL) and creatinine (1.4 mg/dL) on one occasion that were reported as non-serious adverse experiences and resolved completely. These values improved to 30 mg/dL and 0.8 mg/dL, respectively, by the next infusion. Six of the patients had a single, transient elevation in serum transaminases. Two additional patients had persistent elevations in transaminases, ALT and AST, which were present at the initiation of the study, prior to the infusion of GAMMAGARD LIQUID. There was no other evidence of liver abnormalities. None of the hematology or chemistry laboratory abnormalities that occurred during the course of the study required clinical intervention and none had clinical consequences.

During the Phase 3 clinical study, viral safety was assessed by serological screening for HBsAg and antibodies to HCV and HIV-1 and HIV-2 prior to, during, and at the end of the study and by Polymerase Chain Reaction (PCR) tests for HBV, HCV, and HIV-1 genomic sequences prior to and at the end of the study. None of the 61 treated subjects were positive prior to study entry and none converted from negative to positive during the 12-month period of study.

Postmarketing:

The following is a list of adverse reactions that have been identified and reported during the post-approval use of IGIV products:

Respiratory cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular thromboembolism, hypotension
Neurological seizures, tremor
Hematologic hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole pyrexia, rigors
Musculoskeletal back pain
Gastrointestinal hepatic dysfunction, abdominal pain

Rare and Uncommon Adverse Events:

Respiratory apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI)
Integumentary bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson syndrome
Cardiovascular cardiac arrest, vascular collapse
Neurological coma, loss of consciousness
Hematologic pancytopenia, leukopenia

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction to establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently⁴⁶ (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

GAMMAGARD LIQUID should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Only clear or slightly opalescent and colorless or pale yellow solutions are to be administered. GAMMAGARD LIQUID should only be administered intravenously. Other routes of administration have not been evaluated. The use of an in-line filter is optional.

For patients with Primary Immunodeficiency, monthly doses of approximately 300 to 600 mg/kg infused at 3 to 4 week intervals are commonly used.^{23,24} As there are significant differences in the half-life of IgG among patients with Primary Immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical studies.

Rate of Administration

During the first infusion of the Phase 3 clinical study, GAMMAGARD LIQUID was infused at an initial rate of 0.5 mL/kg/hr (0.8 mg/kg/min). The rate was gradually increased every 30 minutes to a rate of 5.0 mL/kg/hr (8.9 mg/kg/min) if it was well tolerated. However, some patients completed the infusion before the maximum rate could be obtained. During subsequent infusions the initial rate and the rate of escalation were based on their previous infusion history; however, the maximum rate attained during the first infusion was used throughout the remainder of the study. The mean rate attained by all patients was 4.3 mL/kg/hr. Fifty-eight subjects (95%) achieved a maximum rate of 4.0 mL/kg/hr or greater and of these, 16 subjects (26%) attained a rate of 5.0 mL/kg/hr.

In general, it is recommended that patients beginning therapy with IGIV or switching from one IGIV product to another be started at the lower rates and then advanced to the maximal rate if they have tolerated several infusions at intermediate rates of infusion. It is important to individualize rates for each patient.

As noted in the WARNINGS section, **patients who have underlying renal disease or who are judged to be at risk of developing thrombotic events should not be infused rapidly with any IGIV product.** Although there are no prospective studies demonstrating that any concentration or rate of infusion is completely safe, it is believed that risk is decreased at lower rates of infusion.⁴⁶ Therefore, as a guideline, it is recommended that these patients who are judged to be at risk of renal dysfunction or thrombotic complications be gradually titrated up to a more conservative maximal rate of less than 3.3 mgIgG/kg/min (< 2mL/kg/hr).

A rate of administration that is too rapid may cause flushing and changes in pulse rate and blood pressure. Slowing or stopping the infusion usually results in the prompt disappearance of signs. The infusion may then be resumed at a rate that is comfortable for the patient.

Drug Interactions

Antibodies in IGIV products may interfere with patient responses to live vaccines, such as those for measles, mumps and rubella.^{47,48,49} The immunizing physician should be informed of recent therapy with IGIV products so that appropriate precautions can be taken.

Admixtures of GAMMAGARD LIQUID with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMMAGARD LIQUID be administered separately from other drugs or medications that the patient may be receiving. The product should not be mixed with IGIV products from other manufacturers.

Normal saline should not be used as a diluent. If dilution is preferred, GAMMAGARD LIQUID may be diluted with 5% dextrose in water (D5W).⁵⁰ No other drug interactions or compatibilities have been evaluated.

HOW SUPPLIED

GAMMAGARD LIQUID is supplied in single use bottles as follows:

NDC Number	Volume	Grams
0944-2700-02	10 mL	1.0
0944-2700-03	25 mL	2.5
0944-2700-04	50 mL	5.0
0944-2700-05	100 mL	10.0
0944-2700-06	200 mL	20.0

STORAGE

Refrigeration: 36 months storage at refrigerated temperature 2° to 8°C (36°-46°F). Do not freeze.

Room Temperature: 12 months storage at room temperature 25°C (77°F), within the first 24 months of the date of manufacture. See below for detailed storage information.

The total storage time of GAMMAGARD LIQUID depends on the point of time the vial is transferred to room temperature. Examples for total storage times are illustrated in Figure 1. The new expiration date must be recorded on the package when the product is transferred to room temperature.

Figure 1: Storage Guidelines
Months from Date of Manufacture

3	6	9	12	15	18	21	24	27	30	33	36	Time in Months
												12 months total
												15 months total
												18 months total
												21 months total
												24 months total
												24 months total
												24 months total
												36 months total

□ 25°C (Room temperature) ■ 2° to 8°C

Storage Details:

- Example 1: If the product is taken out of the refrigerator after 3 months from date of manufacture, it can be stored for 12 months at room temperature. Total storage time is 15 months.
- Example 2: If the product is taken out of the refrigerator after 21 months from the date of manufacture, it can be stored for 3 additional months at room temperature. Total storage time is 24 months.
- After 24 months from date of manufacture, product cannot be stored at room temperature.

To enroll in the confidential, industry-wide Patient Notification System, call 1-888-UPDATE U (1-888-873-2838)

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Westlake Village, CA 91362 USA
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[LE-07-03746; LE-07-03747; LE-07-03748]

Revised October 2009

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GAMMAGARD S/D
[Immune Globulin Intravenous (Human)]
Solvent Detergent Treated
IgA less than 2.2 µg/mL in a 5% Solution

DESCRIPTION

GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV] is a solvent/detergent treated, sterile, freeze-dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. The product is manufactured by the Cohn-Onclay cold ethanol fractionation process followed by ultrafiltration and ion exchange chromatography. Source material for fractionation may be obtained from another U.S. licensed manufacturer. The manufacturing process includes treatment with an organic solvent/detergent mixture,^{1,2} composed of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80.³ The GAMMAGARD S/D manufacturing process provides a significant viral reduction in *in vitro* studies.³ These studies, summarized in Table 1, demonstrate virus clearance during GAMMAGARD S/D manufacturing using infectious human immunodeficiency virus, Types 1 and 2 (HIV-1, HIV-2); bovine viral diarrhea virus (BVD), a model virus for hepatitis C virus; sindbis virus (SIN), a model virus for lipid-enveloped viruses; pseudorabies virus (PRV), a model virus for lipid-enveloped DNA viruses such as herpes; vesicular stomatitis virus (VSV), a model virus for lipid-enveloped RNA viruses; hepatitis A virus (HAV) and encephalomyocarditis virus (EMC), a model virus for non-lipid-enveloped RNA viruses; and porcine parvovirus (PPV), a model virus for non-lipid-enveloped DNA viruses.³ These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during cold ethanol fractionation and the solvent/detergent treatment.³

Process Step Evaluated	Virus Clearance (log ₁₀)								
	Lipid-Enveloped Viruses						Non-Lipid-Enveloped Viruses		
	BVD	HIV-1	HIV-2	PRV	SIN	VSV	EMC	HAV	PPV
Step 1: Processing of Cryo-Poor Plasma to Fraction I-II+III Precipitate	0.6*	5.7	NT	1.0*	NT	NT	NT	0.5*	0.2*
Step 2: Processing of Resuspended Suspension A Precipitate to Suspension B Filter Press Filtrate	1.3	4.9	NT	3.7	NT	NT	3.7	4.1	3.5
Step 3: Processing of Suspension B Filter Press to Suspension B Cuno 70 Filtrate	0.7*	4.0	NT	4.5	NT	NT	3.0	3.9	3.9
Step 4: Solvent/Detergent Treatment	>4.9	>3.7	5.7	>4.1	5.1	6.0	NA	NA	NA
Cumulative Reduction of Virus (log₁₀)	6.2	18.3	5.7	12.3	5.1	6.0	6.7	8.0	7.4

* These values are not included in the computation of the cumulative reduction of virus since the virus clearance is within the variability limit of the assay (±1.0).

NA Not Applicable. Solvent/detergent treatment does not affect non-lipid-enveloped viruses.

NT Not Tested.

When reconstituted with the total volume of diluent (Sterile Water for Injection, USP) supplied, this preparation contains approximately 50 mg of protein per mL (5%), of which at least 90% is gamma globulin. The product, reconstituted to 5%, contains a physiological concentration of sodium chloride (approximately 8.5 mg/mL) and has a pH of 6.8 ± 0.4. Stabilizing agents and additional components are present in the following maximum amounts for a 5% solution: 3 mg/mL Albumin (Human), 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL polyethylene glycol (PEG), 1 µg/mL tri-n-butyl phosphate, 1 µg/mL octoxynol 9, and 100 µg/mL polysorbate 80. The manufacturing process for GAMMAGARD S/D isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. GAMMAGARD S/D contains all of the IgG antibody activities which are present in the donor population. On the average, the distribution of IgG subclasses present in this product is similar to that in normal plasma.³ GAMMAGARD S/D contains trace amounts of IgA (≤ 2.2 µg/mL in a 5% solution). IgM is also present in trace amounts. If it is necessary to prepare a 10% (100 mg/mL) solution for infusion, half the volume of diluent should be added, as described in **DOSAGE AND ADMINISTRATION**. In this case, the stabilizing agents and other components, including IgA, will be present at double the concentrations given for the 5% solution.

GAMMAGARD S/D, Immune Globulin Intravenous (Human) contains no preservative.

CLINICAL PHARMACOLOGY

GAMMAGARD S/D, Immune Globulin Intravenous (Human), contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins.

Peak levels of IgG are reached immediately after infusion of GAMMAGARD S/D. It has been shown that, after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore, a rapid initial drop in serum IgG levels is to be expected.⁴ As a class, IgG survives longer *in vivo* than other serum proteins.^{4,5} Studies show that the half-life of GAMMAGARD S/D is approximately 37.7 ± 15 days.³

Previous studies reported IgG half-life values of 21 to 25 days^{4,5} using radiolabeled IgG or 17.7 to 37.6 days measuring IgG levels during administration of IGIV to immunodeficient patients.⁶ The half-life of IgG can vary considerably from person to person, however. In particular, high concentrations of IgG and hypermetabolism associated with fever and infection have been seen to coincide with a shortened half-life of IgG.^{4,7}

Clinical Study

Clinical studies were conducted with lots of GAMMAGARD S/D containing IgA < 2.2 µg/mL. No clinical studies have been specifically conducted using only lots with IgA content of < 1 µg/mL.

INDICATIONS AND USAGE

GAMMAGARD S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see **WARNINGS**).

Primary Immunodeficiency Diseases

GAMMAGARD S/D is indicated for the treatment of primary immunodeficient states, such as: congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.^{6,7} This indication was supported by a clinical trial of 17 patients with primary immunodeficiency who received a total of 341 infusions. GAMMAGARD S/D is especially useful when high levels or rapid elevation of circulating IgG are desired or when intramuscular injections are contraindicated (e.g., small muscle mass).

B-cell Chronic Lymphocytic Leukemia (CLL)

GAMMAGARD S/D is indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL). In a study of 81 patients, 41 of whom were treated with GAMMAGARD, Immune Globulin Intravenous (Human), bacterial infections were significantly reduced in the treatment group.^{8,9} In this study, the placebo group had approximately twice as many bacterial infections as the IGIV group. The median time to first bacterial infection for the IGIV group was greater than 365 days. By contrast, the time to first bacterial infection in the placebo group was 192 days. The number of viral and fungal infections, which were for the most part minor, was not statistically different between the two groups.

Idiopathic Thrombocytopenic Purpura (ITP)

When a rapid rise in platelet count is needed to prevent and/or to control bleeding in a patient with Idiopathic Thrombocytopenic Purpura, the administration of GAMMAGARD S/D should be considered.

The efficacy of GAMMAGARD has been demonstrated in a clinical study involving 16 patients. Of these 16 patients, 13 had chronic ITP (11 adults, 2 children), and 3 patients had acute ITP (one adult, 2 children). All 16 patients (100%) demonstrated a clinically significant rise in platelet count to a level greater than 40,000/mm³ following the administration of GAMMAGARD. Ten of the 16 patients (62.5%) exhibited a significant rise to greater than 80,000 platelets/mm³. Of these 10 patients, 7 had chronic ITP (5 adults, 2 children), and 3 patients had acute ITP (one adult, 2 children).

The rise in platelet count to greater than 40,000/mm³ occurred after a single 1 g/kg infusion of GAMMAGARD in 8 patients with chronic ITP (6 adults, 2 children), and in 2 patients with acute ITP (one adult, one child). A similar response was observed after two 1 g/kg infusions in 3 adult patients with chronic ITP, and one child with acute ITP. The remaining 2 adult patients with chronic ITP received more than two 1 g/kg infusions before achieving a platelet count greater than 40,000/mm³. The rise in platelet count was generally rapid, occurring within 5 days. However, this rise was transient and not considered curative. Platelet count rises lasted 2 to 3 weeks, with a range of 12 days to 6 months. It should be noted that childhood ITP may resolve spontaneously without treatment.

Kawasaki Syndrome

GAMMAGARD S/D is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome. The percentage incidence of coronary artery aneurysm in patients with Kawasaki syndrome receiving GAMMAGARD either at a single dose of 1 g/kg (n=22) or at a dose of 400 mg/kg for four consecutive days (n=22), beginning within seven days of onset of fever, was 3/44 (6.8%). This was significantly different (p=0.008) from a comparable group of patients that received aspirin only in previous trials and of whom 42/185 (22.7%) experienced coronary artery aneurysms.^{10,11,12} All patients in the GAMMAGARD trial received concomitant aspirin therapy and none experienced hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis).¹³

Several studies have documented the efficacy of intravenous gammaglobulin in reducing the incidence of coronary artery abnormalities resulting from Kawasaki syndrome.^{10-12, 14-17}

CONTRAINDICATIONS

GAMMAGARD S/D is contraindicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see **INDICATIONS AND USAGE** and **WARNINGS**). Patients may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of GAMMAGARD S/D. The occurrence of severe hypersensitivity reactions or anaphylaxis under such conditions should prompt consideration of an alternative therapy.

WARNINGS

Warning

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.¹⁸ Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.*

See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

*GAMMAGARD S/D does not contain sucrose.

GAMMAGARD S/D, Immune Globulin Intravenous (Human), is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. (See DESCRIPTION). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation at 1-800-423-2862 (in the U.S.). The physician should discuss the risks and benefits of this product with the patient.

GAMMAGARD S/D, Immune Globulin Intravenous (Human), should only be administered intravenously. Other routes of administration have not been evaluated.

Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reactions.

GAMMAGARD S/D contains trace amounts of IgA ($\leq 2.2 \mu\text{g/mL}$ in a 5% solution). GAMMAGARD S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern. It should be given with caution to patients with antibodies to IgA or IgA deficiencies, that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated.^{7,19} IGIV preparations depleted of IgA (0.4 to 2.9 $\mu\text{g/mL}$) were shown to be better tolerated by a limited number of patients^{19,46,47} who reacted to IGIV preparations with higher IgA concentrations. However, the concentration of IgA that will not provoke a reaction is not known, and therefore all IGIV preparations carry the risk of inducing an anaphylactoid reaction to IgA. In such instances, a risk of anaphylaxis may exist despite the fact that GAMMAGARD S/D contains trace amounts of IgA.

PRECAUTIONS

General

Some viruses, such as parvovirus B19V (formerly known as parvovirus B19) or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19V most seriously affects pregnant women, or immune-compromised individuals. Symptoms of parvovirus B19V infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) [IGIV] treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per mm^3 , predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL . Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment.

Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of GAMMAGARD S/D and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the rate of infusion to less than 4 mL/kg/hr ($< 3.3 \text{ mg IG/kg/min}$) for a 5% solution or at a rate less than 2 mL/kg/hr ($< 3.3 \text{ mg IG/kg/min}$) for a 10% solution.

Certain components used in the packaging of this product contain natural rubber latex.

Hemolysis

Immune Globulin Intravenous (Human) [IGIV] products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.²⁰⁻²³ Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration²³ (see ADVERSE REACTIONS). IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see PRECAUTIONS: Laboratory Tests).

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema (Transfusion-Related Acute Lung Injury [TRALI]) in patients administered IGIV.²⁴ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see PRECAUTIONS: Laboratory Tests).

Thrombotic Events

Thrombotic events have been reported in association with IGIV²⁵⁻³³ (see ADVERSE REACTIONS). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders and prolonged periods of immobilization. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see PRECAUTIONS: Laboratory Tests). Analysis of adverse event reports^{13,34} has indicated that a rapid rate of infusion may be a risk factor for vascular occlusive events.

Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done (see PRECAUTIONS).

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see PRECAUTIONS).

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see PRECAUTIONS).

Information For Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physician.

Drug Interactions

See DOSAGE AND ADMINISTRATION.

Pregnancy Category C

Animal reproduction studies have not been conducted with GAMMAGARD S/D. It is also not known whether GAMMAGARD S/D can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMMAGARD S/D should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment.³⁵

Types of severe renal adverse reactions that have been seen following IGIV therapy include:

- acute renal failure
- acute tubular necrosis³⁶
- proximal tubular nephropathy
- osmotic nephrosis¹⁸ (see also 37-39)

In general, reported adverse reactions to GAMMAGARD, in patients with either congenital or acquired immunodeficiencies are similar in kind and frequency. Various minor reactions, such as mild to moderate hypotension, headache, fatigue, chills, backache, leg cramps, lightheadedness, fever, urticaria, flushing, slight elevation of blood pressure, nausea and vomiting may occasionally occur. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Immediate anaphylactoid and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reaction (see WARNINGS).

Primary Immunodeficiency Diseases

Twenty-one adverse reactions occurred in 341 infusions (6%), when using GAMMAGARD (5% solution), in a clinical trial of 17 patients with primary immunodeficiency.⁴⁰ Of the 17 patients, 12 (71%) were adults, and 5 (29%) were children (16 years or younger).

In a cross-over study comparing GAMMAGARD and GAMMAGARD S/D (5% solutions) conducted in a small number ($n=10$) of primary immunodeficient patients, no unusual or unexpected adverse reactions were observed in the GAMMAGARD S/D group. The adverse reactions experienced in the GAMMAGARD S/D group were similar in frequency and nature to those observed in the control group consisting of patients receiving GAMMAGARD.

GAMMAGARD, reconstituted to a concentration of 10%, was administered intravenously at rates varying from 2 to 11 mL/kg/hr . Systemic reactions occurred in 23 (10.5%) of 219 infusions. This compares with an adverse reaction incidence of 6% (only systemic reactions reported) for primary immunodeficient patients previously treated with a 5% solution at infusion rates varying between 2 and 8 mL/kg/hr , as described above (see reference 40). Local pain or irritation was experienced during 35 (16%) of 219 infusions. Application of a warm compress to the infusion site alleviated local symptoms. These local reactions tended to be associated with hand vein infusions and their incidence may be reduced by infusions via the antecubital vein.

B-cell Chronic Lymphocytic Leukemia (CLL)

In the study of patients with B-cell Chronic Lymphocytic Leukemia, the incidence of adverse reactions associated with GAMMAGARD infusions was approximately 1.3% while that associated with placebo (normal saline) infusions was 0.6%.⁹

Idiopathic Thrombocytopenic Purpura (ITP)

During the clinical study of GAMMAGARD for the treatment of Idiopathic Thrombocytopenic Purpura, the only adverse reaction reported was headache which occurred in 12 of 16 patients (75%). Of these 12 patients, 11 had chronic ITP (9 adults, 2 children), and one child had acute ITP. Oral antihistamines and analgesics alleviated the symptoms and were used as pretreatment for those patients requiring additional IGIV therapy. The remaining 4 patients did not report any side effects and did not require pretreatment.

Kawasaki Syndrome

In a study of patients (n=51) with Kawasaki syndrome, no hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis) were reported in patients receiving either a single 1 g/kg dose of IGIV, GAMMAGARD, or 400 mg/kg of IGIV, GAMMAGARD, for four consecutive days.¹³ Mild adverse reactions, including chills, flushing, cramping, headache, hypotension, nausea, rash and wheezing, were reported with both dose regimens. These adverse reactions occurred in 7/51 (13.7%) patients and in association with 7/129 (5.4%) infusions. Of the 25 patients who received a single 1 g/kg dose, 4 patients experienced adverse reactions for an incidence of 16%. Of the 26 patients who received 400 mg/kg/day over 4 days, 3 experienced a single adverse reaction for an incidence of 11.5%.³

Postmarketing:

The following is a list of adverse reactions that have been identified and reported during the post-approval use of IGIV products:

Respiratory cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular thromboembolism, hypotension
Neurological seizures, tremor
Hematologic hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole pyrexia, rigors
Musculoskeletal back pain
Gastrointestinal hepatic dysfunction, abdominal pain

Rare and Uncommon Adverse Events:

Respiratory apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI)
Integumentary bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson syndrome
Cardiovascular cardiac arrest, vascular collapse
Neurological coma, loss of consciousness
Hematologic pancytopenia, leukopenia

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently⁴¹ (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Primary Immunodeficiency Diseases

For patients with primary immunodeficiencies, monthly doses of approximately 300-600 mg/kg infused at 3 to 4 week intervals are commonly used.^{42,43} As there are significant differences in the half-life of IgG among patients with primary immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical trials.

B-cell Chronic Lymphocytic Leukemia (CLL)

For patients with hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell Chronic Lymphocytic Leukemia, a dose of 400 mg/kg every 3 to 4 weeks is recommended.

Kawasaki Syndrome

For patients with Kawasaki syndrome, either a single 1 g/kg dose or a dose of 400 mg/kg for four consecutive days beginning within seven days of the onset of fever, administered concomitantly with appropriate aspirin therapy (80-100 mg/kg/day in four divided doses) is recommended.⁴⁴

Idiopathic Thrombocytopenic Purpura (ITP)

For patients with acute or chronic Idiopathic Thrombocytopenic Purpura, a dose of 1 g/kg is recommended. The need for additional doses can be determined by clinical response and platelet count. Up to three separate doses may be given on alternate days if required.

No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, the recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in the literature in order to reduce the risk of acute renal failure.⁴⁵

Reconstitution: Use Aseptic Technique

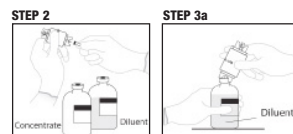
When reconstitution is performed aseptically **outside** of a sterile laminar air flow hood, administration should begin as soon as possible, but not more than 2 hours after reconstitution.

When reconstitution is performed aseptically **inside** of a sterile laminar air flow hood, the reconstituted product may be either maintained in the original glass container or pooled into VIAFLEX bags and stored under constant refrigeration (2-8°C), for up to 24 hours. (The date and time of reconstitution/pooling should be recorded). If these conditions are not met, sterility of the reconstituted product cannot be maintained. Partially used vials should be discarded.

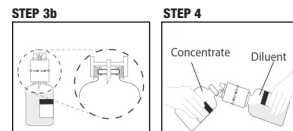
A. 5% Solution

Note: If refrigerated, allow GAMMAGARD S/D to reach room temperature before administration.

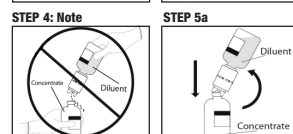
1. Remove bottle caps and clean stoppers with germicidal solution.
2. Remove spike cap from one end of the transfer device. Do not touch spike.
- 3a. Place diluent bottle on a flat surface. Use exposed end of transfer device to spike diluent bottle through center of the stopper.



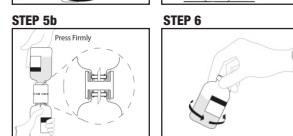
- CAUTION: Failure to insert spike into center of the stopper may result in dislodging of the stopper.**
- 3b. Ensure that the collar collapses fully into the device by pushing down on the transfer device firmly.



- While holding onto transfer device, remove remaining spike cover. Do not touch spike.
4. Hold diluent bottle with attached transfer device at an angle to the concentrate bottle to prevent spilling the diluent.



- Note: Do not hold diluent bottle upside down, for this can lead to diluent spillage.**
- 5a. Spike concentrate bottle through center of the stopper while **quickly inverting the diluent vial** to minimize spilling out diluent.



- CAUTION: Failure to insert the spike into the center of the stopper may result in dislodging of the stopper and loss of vacuum.**

- 5b. Ensure that the collar collapses fully into the device by pushing down on the diluent bottle firmly.
6. After transfer of diluent is complete, remove transfer device and empty diluent bottle. Immediately swirl the concentrate bottle gently to thoroughly mix contents.

CAUTION: Do not shake. Avoid foaming.

Discard transfer device after single use per local guidelines.

B. 10% Solution

1. Follow step 1 as previously described in **A**.
2. To prepare a 10% solution, it is necessary to remove half of the volume of diluent. Table 2 indicates the volume of diluent that should be **removed from the vial** before attaching the transfer device to produce a 10% concentration. Using aseptic technique, withdraw the unnecessary volume of diluent using a sterile hypodermic syringe and needle. Discard the filled syringe into a suitable puncture proof container (Sharps Container).
3. Using the residual diluent in the diluent vial, follow steps 2-6 as previously described in **A**.

Concentration	5 g bottle	10 g bottle
5%	Do not remove any diluent for reconstitution of 5% Solution	
10%	48 mL	96 mL

Rate of Administration

It is recommended that initially a 5% solution be infused at a rate of 0.5 mL/kg/Hr. If infusion at this rate and concentration causes the patient no distress, the administration rate may be gradually increased to a maximum rate of 4 mL/kg/Hr for patients with no history of adverse reactions to IGIV and no significant risk factors for renal dysfunction or thrombotic complications. Patients who tolerate the 5% concentration at 4 mL/kg/Hr can be infused with the 10% concentration starting at 0.5 mL/kg/Hr. If no adverse effects occur, the rate can be increased gradually up to a maximum of 8 mL/kg/Hr.

In general, it is recommended that patients beginning therapy with IGIV or switching from one IGIV product to another be started at the lower rates of infusion and should be advanced to the maximal rate only after they have tolerated several infusions at intermediate rates of infusion. It is important to individualize rates for each patient. As noted in the **WARNINGS** section, **patients who have underlying renal disease or who are judged to be at risk of developing thrombotic events should not be infused rapidly with any IGIV product.**

Although there are no prospective studies demonstrating that any concentration or rate of infusion is completely safe, it is believed that risk may be decreased at lower rates of infusion.⁴⁵ Therefore, as a guideline, it is recommended that these patients who are judged to be at risk of renal dysfunction or thrombotic complications be gradually titrated up to a more conservative maximal rate of less than 3.3 mg/kg/min (< 2 mL/kg/hr of a 10% or < 4 mL/kg/hr of a 5% solution).

It is recommended that antecubital veins be used especially for 10% solutions, if possible. This may reduce the likelihood of the patient experiencing discomfort at the infusion site (see **ADVERSE REACTIONS**).

A rate of administration which is too rapid may cause flushing and changes in pulse rate and blood pressure. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Drug Interactions

Admixtures of GAMMAGARD S/D, Immune Globulin Intravenous (Human), with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMMAGARD S/D be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with Immune Globulin Intravenous (Human) from other manufacturers.

Antibodies in immune globulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, and rubella. The immunizing physician should be informed of recent therapy with Immune Globulin Intravenous (Human) so that appropriate precautions can be taken.

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Administration

GAMMAGARD S/D should be administered as soon after reconstitution as possible, or as described in **DOSAGE AND ADMINISTRATION**.

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstituted material should be a clear to slightly opalescent and colorless to pale yellow solution. Do not use if particulate matter and/or discoloration is observed.

Follow directions for use which accompany the administration set provided. If another administration set is used, ensure that the set contains a similar filter.

HOW SUPPLIED

GAMMAGARD S/D is supplied in 2.5 g (NDC number 0944-2620-02), 5 g (NDC number 0944-2620-03), or 10 g (NDC number 0944-2620-04) single use bottles. Each bottle of GAMMAGARD S/D is furnished with a suitable volume of Sterile Water for Injection, USP, a transfer device and an administration set which contains an integral airway and a 15 micron filter.

STORAGE

GAMMAGARD S/D is to be stored at a temperature not to exceed 25°C (77°F). Freezing should be avoided to prevent the diluent bottle from breaking.

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Revised December 2009

Baxter

GAMMAGARD S/D [Immune Globulin Intravenous (Human)]

Solvent Detergent Treated

IgA less than 1 µg/mL in a 5% solution

DESCRIPTION

GAMMAGARD S/D Immune Globulin Intravenous (Human) [IGIV], IgA less than 1 µg/mL in a 5% Solution (IgA < 1 µg/mL), is GAMMAGARD S/D, selected to have an IgA concentration of less than 1 µg/mL of IgA in a 5% solution. GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV] is a solvent/detergent treated, sterile, freeze-dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. The product is manufactured by the Cohn-Onclay cold ethanol fractionation process followed by ultrafiltration and ion exchange chromatography. Source material for fractionation may be obtained from another U.S. licensed manufacturer. The manufacturing process includes treatment with an organic solvent/detergent mixture,^{1,2} composed of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80.³ The GAMMAGARD S/D manufacturing process provides a significant viral reduction in *in vitro* studies.³ These studies, summarized in Table 1, demonstrate virus clearance during GAMMAGARD S/D manufacturing using infectious human immunodeficiency virus, Types 1 and 2 (HIV-1, HIV-2); bovine viral diarrhea virus (BVD), a model virus for hepatitis C virus; sindbis virus (SIN), a model virus for lipid-enveloped viruses; pseudorabies virus (PRV), a model virus for lipid-enveloped DNA viruses such as herpes; vesicular stomatitis virus (VSV), a model virus for lipid-enveloped RNA viruses; hepatitis A virus (HAV) and encephalomyocarditis virus (EMC), a model virus for non-lipid-enveloped RNA viruses; and porcine parvovirus (PPV), a model virus for non-lipid-enveloped DNA viruses.³ These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during cold ethanol fractionation and the solvent/detergent treatment.³

Process Step Evaluated	Virus Clearance (log ₁₀)								
	Lipid-Enveloped Viruses						Non-Lipid-Enveloped Viruses		
	BVD	HIV-1	HIV-2	PRV	SIN	VSV	EMC	HAV	PPV
Step 1: Processing of Cryo-Poor Plasma to Fraction I+II+III Precipitate	0.6*	5.7	NT	1.0*	NT	NT	NT	0.5*	0.2*
Step 2: Processing of Resuspended Suspension A Precipitate to Suspension B Filter Press Filtrate	1.3	4.9	NT	3.7	NT	NT	3.7	4.1	3.5
Step 3: Processing of Suspension B Filter Press to Suspension B Cuno 70 Filtrate	0.7*	4.0	NT	4.5	NT	NT	3.0	3.9	3.9
Step 4: Solvent/Detergent Treatment	>4.9	>3.7	5.7	>4.1	5.1	6.0	NA	NA	NA
Cumulative Reduction of Virus (log ₁₀)	6.2	18.3	5.7	12.3	5.1	6.0	6.7	8.0	7.4

* These values are not included in the computation of the cumulative reduction of virus since the virus clearance is within the variability limit of the assay (≤ 1.0).

NA Not Applicable. Solvent/detergent treatment does not affect non-lipid-enveloped viruses.

NT Not Tested.

When reconstituted with the total volume of diluent (Sterile Water for Injection, USP) supplied, this preparation contains approximately 50 mg of protein per mL (5%), of which at least 90% is gamma globulin. The product, reconstituted to 5%, contains a physiological concentration of sodium chloride (approximately 8.5 mg/mL) and has a pH of 6.8 ± 0.4 . Stabilizing agents and additional components are present in the following maximum amounts for a 5% solution: 3 mg/mL Albumin (Human), 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL polyethylene glycol (PEG), 1 µg/mL tri-n-butyl phosphate, 1 µg/mL octoxynol 9, and 100 µg/mL polysorbate 80. The manufacturing process for GAMMAGARD S/D, isolates IgG without additional chemical or enzymatic modification, and the Fc portion is maintained intact. GAMMAGARD S/D contains all of the IgG antibody activities which are present in the donor population. On the average, the distribution of IgG subclasses present in this product is similar to that in normal plasma.³ GAMMAGARD S/D, IgA < 1 µg/mL, contains trace amounts of IgA (less than 1 µg/mL in a 5% solution). IgM is also present in trace amounts. If it is necessary to prepare a 10% (100 mg/mL) solution for infusion, half the volume of diluent should be added, as described in **DOSE AND ADMINISTRATION**. In this case, the stabilizing agents and other components, including IgA, will be present at double the concentrations given for the 5% solution. GAMMAGARD S/D, Immune Globulin Intravenous (Human) contains no preservative.

CLINICAL PHARMACOLOGY

GAMMAGARD S/D, Immune Globulin Intravenous (Human), contains a broad spectrum of IgG antibodies against bacterial and viral agents that are capable of opsonization and neutralization of microbes and toxins.

Peak levels of IgG are reached immediately after infusion of GAMMAGARD S/D. It has been shown that, after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore, a rapid initial drop in serum IgG levels is to be expected.⁴ As a class, IgG survives longer *in vivo* than other serum proteins.^{4,5} Studies show that the half-life of GAMMAGARD S/D is approximately 37.7 ± 15 days.³

Previous studies reported IgG half-life values of 21 to 25 days^{4,5} using radiolabeled IgG or 17.7 to 37.6 days measuring IgG levels during administration of IGIV to immunodeficient patients.⁶ The half-life of IgG can vary considerably from person to person, however. In particular, high concentrations of IgG and hypermetabolism associated with fever and infection have been seen to coincide with a shortened half-life of IgG.^{4,7}

Clinical Study

Clinical studies were conducted with lots of GAMMAGARD S/D containing IgA < 2.2 µg/mL. No clinical studies have been specifically conducted using only lots with IgA content of < 1 µg/mL.

INDICATIONS AND USAGE

GAMMAGARD S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see **WARNINGS**).

Primary Immunodeficiency Diseases

GAMMAGARD S/D is indicated for the treatment of primary immunodeficient states, such as: congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.^{6,7} This indication was supported by a clinical trial of 17 patients with primary immunodeficiency who received a total of 341 infusions. GAMMAGARD S/D is especially useful when high levels or rapid elevation of circulating IgG are desired or when intramuscular injections are contraindicated (e.g., small muscle mass).

B-cell Chronic Lymphocytic Leukemia (CLL)

GAMMAGARD S/D is indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL). In a study of 81 patients, 41 of whom were treated with GAMMAGARD, Immune Globulin Intravenous (Human), bacterial infections were significantly reduced in the treatment group.^{8,9} In this study, the placebo group had approximately twice as many bacterial infections as the IGIV group. The median time to first bacterial infection for the IGIV group was greater than 365 days. By contrast, the time to first bacterial infection in the placebo group was 192 days. The number of viral and fungal infections, which were for the most part minor, was not statistically different between the two groups.

Idiopathic Thrombocytopenic Purpura (ITP)

When a rapid rise in platelet count is needed to prevent and/or to control bleeding in a patient with Idiopathic Thrombocytopenic Purpura, the administration of GAMMAGARD S/D, should be considered.

The efficacy of GAMMAGARD has been demonstrated in a clinical study involving 16 patients. Of these 16 patients, 13 had chronic ITP (11 adults, 2 children), and 3 patients had acute ITP (one adult, 2 children). All 16 patients (100%) demonstrated a clinically significant rise in platelet count to a level greater than 40,000/mm³ following the administration of GAMMAGARD. Ten of the 16 patients (62.5%) exhibited a significant rise to greater than 80,000 platelets/mm³. Of these 10 patients, 7 had chronic ITP (5 adults, 2 children), and 3 patients had acute ITP (one adult, 2 children).

The rise in platelet count to greater than 40,000/mm³ occurred after a single 1 g/kg infusion of GAMMAGARD in 8 patients with chronic ITP (6 adults, 2 children), and in 2 patients with acute ITP (one adult, one child). A similar response was observed after two 1 g/kg infusions in 3 adult patients with chronic ITP, and one child with acute ITP. The remaining 2 adult patients with chronic ITP received more than two 1 g/kg infusions before achieving a platelet count greater than 40,000/mm³. The rise in platelet count was generally rapid, occurring within 5 days. However, this rise was transient and not considered curative. Platelet count rises lasted 2 to 3 weeks, with a range of 12 days to 6 months. It should be noted that childhood ITP may resolve spontaneously without treatment.

Kawasaki Syndrome

GAMMAGARD S/D is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome. The percentage incidence of coronary artery aneurysm in patients with Kawasaki syndrome receiving GAMMAGARD either at a single dose of 1 g/kg (n=22) or at a dose of 400 mg/kg for four consecutive days (n=22), beginning within seven days of onset of fever, was 3/44 (6.8%). This was significantly different (p=0.008) from a comparable group of patients that received aspirin only in previous trials and of whom 42/185 (22.7%) experienced coronary artery aneurysms.^{10,11,12} All patients in the GAMMAGARD trial received concomitant aspirin therapy and none experienced hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis).¹³

Several studies have documented the efficacy of intravenous gammaglobulin in reducing the incidence of coronary artery abnormalities resulting from Kawasaki syndrome.^{10-12, 14-17}

CONTRAINDICATIONS

GAMMAGARD S/D is contraindicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see **INDICATIONS AND USAGE** and **WARNINGS**). Patients may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of GAMMAGARD S/D. The occurrence of severe hypersensitivity reactions or anaphylaxis under such conditions should prompt consideration of an alternative therapy.

Baxter

WARNINGS

Warning

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.¹⁸ Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.*

See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections for important information intended to reduce the risk of acute renal failure.

*GAMMAGARD S/D does not contain sucrose.

GAMMAGARD S/D, Immune Globulin Intravenous (Human) is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. (See **DESCRIPTION**). Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation at 1-800-423-2862 (in the U.S.). The physician should discuss the risks and benefits of this product with the patient.

GAMMAGARD S/D, Immune Globulin Intravenous (Human), should only be administered intravenously. Other routes of administration have not been evaluated.

Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reactions.

GAMMAGARD S/D, IgA < 1 µg/mL, contains trace amounts of IgA (less than 1 µg/mL in a 5% solution). GAMMAGARD S/D is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern. It should be given with caution to patients with antibodies to IgA or IgA deficiencies, that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated.^{7,19} GAMMAGARD S/D, IgA < 1 µg/mL, has an IgA concentration less than 1 µg/mL. GAMMAGARD S/D has an IgA concentration less than or equal to 2.2 µg/mL. IGIV preparations depleted of IgA (0.4 to 2.9 µg/mL) were shown to be better tolerated by a limited number of patients^{19,46,47} who reacted to IGIV preparations with higher IgA concentrations. However, the concentration of IgA that will not provoke a reaction is not known, and therefore all IGIV preparations carry the risk of inducing an anaphylactic reaction to IgA. In such instances, a risk of anaphylaxis may exist despite the fact that GAMMAGARD S/D, IgA < 1 µg/mL, contains trace amounts of IgA.

PRECAUTIONS

General

Some viruses, such as B19V (formerly known as parvovirus B19) or hepatitis A, are particularly difficult to remove or inactivate at this time. B19V most seriously affects pregnant women, or immune-compromised individuals. Symptoms of B19V infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting, and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) [IGIV] treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IGIV treatment. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assume that patients are not volume depleted prior to the initiation of the infusion of IGIV. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of GAMMAGARD S/D and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the rate of infusion to less than 4 mL/kg/Hr (<3.3 mg IG/kg/min) for a 5% solution or at a rate less than 2 mL/kg/Hr (< 3.3 mg IG/kg/min) for a 10% solution.

Certain components used in the packaging of this product contain natural rubber latex.

Hemolysis

Immune Globulin Intravenous (Human) [IGIV] products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.²⁰⁻²³ Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration²³ (see **ADVERSE REACTIONS**). IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (see **PRECAUTIONS: Laboratory Tests**).

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema (Transfusion-Related Acute Lung Injury [TRALI]) in patients administered IGIV.²⁴ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see **PRECAUTIONS: Laboratory Tests**).

Thrombotic Events

Thrombotic events have been reported in association with IGIV²⁵⁻³³ (see **ADVERSE REACTIONS**). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity, hypercoagulable disorders and prolonged periods of immobilization. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see **PRECAUTIONS: Laboratory Tests**). Analysis of adverse event reports^{13,34} has indicated that a rapid rate of infusion may be a risk factor for vascular occlusive events.

Laboratory Tests

If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be done (see **PRECAUTIONS**).

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see **PRECAUTIONS**).

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see **PRECAUTIONS**).

Information For Patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physician.

Drug Interactions

See **DOSAGE AND ADMINISTRATION**.

Pregnancy Category C

Animal reproduction studies have not been conducted with GAMMAGARD S/D, Immune Globulin Intravenous (Human). It is also not known whether GAMMAGARD S/D can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMMAGARD S/D should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment.³⁵

Types of severe renal adverse reactions that have been seen following IGIV therapy include:

- acute renal failure
- acute tubular necrosis³⁶
- proximal tubular nephropathy
- osmotic nephrosis¹⁸ (see also 37-39)

In general, reported adverse reactions to GAMMAGARD, in patients with either congenital or acquired immunodeficiencies are similar in kind and frequency. Various minor reactions, such as mild to moderate hypotension, headache, fatigue, chills, backache, leg cramps, lightheadedness, fever, urticaria, flushing, slight elevation of blood pressure, nausea and vomiting may occasionally occur. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reaction (see **WARNINGS**).

Primary Immunodeficiency Diseases

Twenty-one adverse reactions occurred in 341 infusions (6%), when using GAMMAGARD (5% solution), in a clinical trial of 17 patients with primary immunodeficiency.⁴⁰ Of the 17 patients, 12 (71%) were adults, and 5 (29%) were children (16 years or younger).

In a cross-over study comparing GAMMAGARD and GAMMAGARD S/D (5% solutions) conducted in a small number (n=10) of primary immunodeficient patients, no unusual or unexpected adverse reactions were observed in the GAMMAGARD S/D group. The adverse reactions experienced in the GAMMAGARD S/D group were similar in frequency and nature to those observed in the control group consisting of patients receiving GAMMAGARD.

GAMMAGARD, reconstituted to a concentration of 10%, was administered intravenously at rates varying from 2 to 11 mL/kg/Hr. Systemic reactions occurred in 23 (10.5%) of 219 infusions. This compares with an adverse reaction incidence of 6% (only systemic reactions reported) for primary immunodeficient patients previously treated with a 5% solution at infusion rates varying between 2 and 8 mL/kg/Hr, as described above (see reference 40). Local pain or irritation was experienced during 35 (16%) of 219 infusions. Application of a warm compress to the infusion site alleviated local symptoms. These local reactions tended to be associated with hand vein infusions and their incidence may be reduced by infusions via the antecubital vein.

B-cell Chronic Lymphocytic Leukemia (CLL)

In the study of patients with B-cell Chronic Lymphocytic Leukemia, the incidence of adverse reactions associated with GAMMAGARD infusions was approximately 1.3% while that associated with placebo (normal saline) infusions was 0.6%.⁹

Idiopathic Thrombocytopenic Purpura (ITP)

During the clinical study of GAMMAGARD for the treatment of Idiopathic Thrombocytopenic Purpura, the only adverse reaction reported was headache which occurred in 12 of 16 patients (75%). Of these 12 patients, 11 had chronic ITP (9 adults, 2 children), and one child had acute ITP. Oral antihistamines and analgesics alleviated the symptoms and were used as pretreatment for those patients requiring additional IGIV therapy. The remaining 4 patients did not report any side effects and did not require pretreatment.

Kawasaki Syndrome

In a study of patients (n=51) with Kawasaki syndrome, no hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis) were reported in patients receiving either a single 1 g/kg dose of IGIV, GAMMAGARD, or 400 mg/kg of IGIV, GAMMAGARD, for four consecutive days.¹³ Mild adverse reactions, including chills, flushing, cramping, headache, hypotension, nausea, rash and wheezing, were reported with both dose regimens. These adverse reactions occurred in 7/51 (13.7%) patients and in association with 7/129 (5.4%) infusions. Of the 25 patients who received a single 1 g/kg dose, 4 patients experienced adverse reactions for an incidence of 16%. Of the 26 patients who received 400 mg/kg/day over 4 days, 3 experienced a single adverse reaction for an incidence of 11.5%.³

Postmarketing:

The following is a list of adverse reactions that have been identified and reported during the post-approval use of IGIV products:

Respiratory
cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular
thromboembolism, hypotension
Neurological
seizures, tremor
Hematologic
hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole
pyrexia, rigors
Musculoskeletal
back pain
Gastrointestinal
hepatic dysfunction, abdominal pain

Rare and Uncommon Adverse Events:

Respiratory
apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI)
Integumentary
bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson syndrome
Cardiovascular
cardiac arrest, vascular collapse
Neurological
coma, loss of consciousness
Hematologic
pancytopenia, leukopenia

Because postmarketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently⁴¹ (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Primary Immunodeficiency Diseases

For patients with primary immunodeficiencies, monthly doses of approximately 300-600 mg/kg infused at 3 to 4 week intervals are commonly used.^{42,43} As there are significant differences in the half-life of IgG among patients with primary immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical trials.

B-cell Chronic Lymphocytic Leukemia (CLL)

For patients with hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell Chronic Lymphocytic Leukemia, a dose of 400 mg/kg every 3 to 4 weeks is recommended.

Kawasaki Syndrome

For patients with Kawasaki syndrome, either a single 1 g/kg dose or a dose of 400 mg/kg for four consecutive days beginning within seven days of the onset of fever, administered concomitantly with appropriate aspirin therapy (80-100 mg/kg/day in four divided doses) is recommended.⁴⁴

Idiopathic Thrombocytopenic Purpura (ITP)

For patients with acute or chronic Idiopathic Thrombocytopenic Purpura, a dose of 1 g/kg is recommended. The need for additional doses can be determined by clinical response and platelet count. Up to three separate doses may be given on alternate days if required.

No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, the recommended doses should not be exceeded and the concentration and infusion rate selected should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in the literature in order to reduce the risk of acute renal failure.⁴⁵

Reconstitution: Use Aseptic Technique

When reconstitution is performed aseptically **outside** of a sterile laminar air flow hood, administration should begin as soon as possible, but not more than 2 hours after reconstitution.

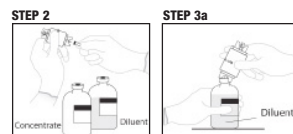
When reconstitution is performed aseptically **inside** of a sterile laminar air flow hood, the reconstituted product may be either maintained in the original glass container or pooled into VIAFLEX bags and stored under constant refrigeration (2-8°C), for up to 24 hours. (The date and time of reconstitution/pooling should be recorded). If these conditions are not met, sterility of the reconstituted product cannot be maintained.

Partially used vials should be discarded.

A. 5% Solution

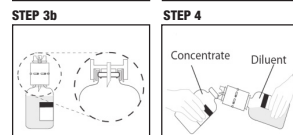
Note: If refrigerated, allow GAMMAGARD S/D to reach room temperature before administration.

1. Remove bottle caps and clean stoppers with germicidal solution.
2. Remove spike cap from one end of the transfer device. Do not touch spike.
- 3a. Place diluent bottle on a flat surface. Use exposed end of transfer device to spike diluent bottle through center of the stopper.



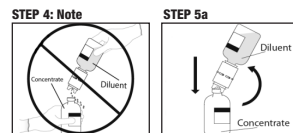
CAUTION: Failure to insert spike into center of the stopper may result in dislodging of the stopper.

- 3b. Ensure that the collar collapses fully into the device by pushing down on the transfer device firmly.
4. Hold diluent bottle with attached transfer device at an angle to the concentrate bottle to prevent spilling the diluent.

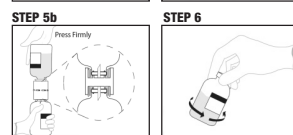


Note: Do not hold diluent bottle upside down, for this can lead to diluent spillage.

- 5a. Spike concentrate bottle through center of the stopper while **quickly inverting the diluent vial** to minimize spilling out diluent.



- 5b. Ensure that the collar collapses fully into the device by pushing down on the diluent bottle firmly.
6. After transfer of diluent is complete, remove transfer device and empty diluent bottle. Immediately swirl the concentrate bottle gently to thoroughly mix contents.



CAUTION: Do not shake. Avoid foaming.

Discard transfer device after single use per local guidelines.

B. 10% Solution

1. Follow step 1 as previously described in **A**.
2. To prepare a 10% solution, it is necessary to remove half of the volume of diluent. **Table 2** indicates the volume of diluent that should be **removed from the vial** before attaching the transfer device to produce a 10% concentration. Using aseptic technique, withdraw the unnecessary volume of diluent using a sterile hypodermic syringe and needle. Discard the filled syringe into a suitable puncture proof container (Sharps Container).
3. Using the residual diluent in the diluent vial, follow steps 2-6 as previously described in **A**.

Table 2 Required Diluent Volume to Be Removed		
Concentration	5 g bottle	10 g bottle
5%	Do not remove any diluent for reconstitution of 5% Solution	
10%	48 mL	96 mL

Rate of Administration

It is recommended that initially a 5% solution be infused at a rate of 0.5 mL/kg/Hr. If infusion at this rate and concentration causes the patient no distress, the administration rate may be gradually increased to a maximum rate of 4 mL/kg/Hr for patients with no history of adverse reactions to IGIV and no significant risk factors for renal dysfunction or thrombotic complications. Patients who tolerate the 5% concentration at 4 mL/kg/Hr can be infused with the 10% concentration starting at 0.5 mL/kg/Hr. If no adverse effects occur, the rate can be increased gradually up to a maximum of 8 mL/kg/Hr.

In general, it is recommended that patients beginning therapy with IGIV or switching from one IGIV product to another be started at the lower rates of infusion and should be advanced to the maximal rate only after they have tolerated several infusions at intermediate rates of infusion. It is important to individualize rates for each patient. As noted in the **WARNINGS** section, **patients who have underlying renal disease or who are judged to be at risk of developing thrombotic events should not be infused rapidly with any IGIV product.**

Although there are no prospective studies demonstrating that any concentration or rate of infusion is completely safe, it is believed that risk may be decreased at lower rates of infusion.⁴⁵ Therefore, as a guideline, it is recommended that these patients who are judged to be at risk of renal dysfunction or thrombotic complications be gradually titrated up to a more conservative maximal rate of less than 3.3 mg/kg/min (< 2 mL/kg/hr of a 10% or < 4 mL/kg/hr of a 5% solution).

It is recommended that antecubital veins be used especially for 10% solutions, if possible. This may reduce the likelihood of the patient experiencing discomfort at the infusion site (see **ADVERSE REACTIONS**).

A rate of administration which is too rapid may cause flushing and changes in pulse rate and blood pressure. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Drug Interactions

Admixtures of GAMMAGARD S/D, Immune Globulin Intravenous (Human), with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMMAGARD S/D be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with Immune Globulin Intravenous (Human) from other manufacturers. Antibodies in immune globulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, and rubella. The immunizing physician should be informed of recent therapy with Immune Globulin Intravenous (Human) so that appropriate precautions can be taken.

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Administration

GAMMAGARD S/D should be administered as soon after reconstitution as possible, or as described in **DOSE AND ADMINISTRATION**.

The reconstituted material should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstituted material should be a clear to slightly opalescent and colorless to pale yellow solution. Do not use if particulate matter and/or discoloration is observed.

Follow directions for use which accompany the administration set provided. If another administration set is used, ensure that the set contains a similar filter.

HOW SUPPLIED

GAMMAGARD S/D with an IgA concentration of less than 1 µg/mL in a 5% solution is supplied in 5 g (NDC number 0944-2655-03), or 10 g (NDC number 0944-2655-04) single use bottles. Each bottle of GAMMAGARD S/D is furnished with a suitable volume of Sterile Water for Injection, USP, a transfer device and an administration set which contains an integral airway and a 15 micron filter.

STORAGE

GAMMAGARD S/D is to be stored at a temperature not to exceed 25°C (77°F). Freezing should be avoided to prevent the diluent bottle from breaking.

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Approved December 2009