

# 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,<sup>1,2</sup> composed of tri-n-butyl phosphate, octoxynol 9 and polysorbate 80.<sup>3</sup> The GAMMAGARD S/D manufacturing process provides a significant viral reduction in *in vitro* studies.<sup>3</sup> 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.<sup>3</sup> These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during cold ethanol fractionation and the solvent/detergent treatment.<sup>3</sup>

Process Step Evaluated	Virus Clearance (log <sub>10</sub> )								
	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 Filtrate 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 <sub>10</sub> )	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 ( $\leq 1.0$ ).

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  $6.8 \pm 0.4$ . 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.<sup>3</sup> GAMMAGARD S/D contains trace amounts of IgA ( $\leq 2.2$  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.<sup>4</sup> As a class, IgG survives longer *in vivo* than other serum proteins.<sup>4,5</sup> Studies show that the half-life of GAMMAGARD S/D is approximately  $37.7 \pm 15$  days.<sup>3</sup>

Previous studies reported IgG half-life values of 21 to 25 days<sup>4,5</sup> using radiolabeled IgG or 17.7 to 37.6 days measuring IgG levels during administration of IGIV to immunodeficient patients.<sup>6</sup> 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.<sup>4,7</sup>

## 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.<sup>6,7</sup> 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.<sup>8,9</sup> 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/mm<sup>3</sup> following the administration of GAMMAGARD. Ten of the 16 patients (62.5%) exhibited a significant rise to greater than 80,000 platelets/mm<sup>3</sup>. 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/mm<sup>3</sup> 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/mm<sup>3</sup>. 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.<sup>10,11,12</sup> All patients in the GAMMAGARD trial received concomitant aspirin therapy and none experienced hypersensitivity-type reactions (urticaria, bronchospasm or generalized anaphylaxis).<sup>13</sup>

Several studies have documented the efficacy of intravenous gammaglobulin in reducing the incidence of coronary artery abnormalities resulting from Kawasaki syndrome.<sup>10-12, 14-17</sup>

## 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.<sup>18</sup> 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.<sup>7,19</sup> 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<sup>19,46,47</sup> 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  $\text{mm}^3$ , predominantly from the granulocytic series, and elevated protein levels up to several hundred  $\text{mg/dL}$ . 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.<sup>20-23</sup> Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration<sup>23</sup> (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.<sup>24</sup> 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<sup>25-33</sup> (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<sup>13,34</sup> 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.<sup>35</sup>

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

- acute renal failure
- acute tubular necrosis<sup>36</sup>
- proximal tubular nephropathy
- osmotic nephrosis<sup>18</sup> (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.<sup>40</sup> 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%.<sup>9</sup>

## 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.<sup>13</sup> 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%.<sup>3</sup>

## Postmarketing:

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

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

## Rare and Uncommon Adverse Events:

<b>Respiratory</b>	apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Associated Lung Injury (TRALI)
<b>Integumentary</b>	bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson syndrome
<b>Cardiovascular</b>	cardiac arrest, vascular collapse
<b>Neurological</b>	coma, loss of consciousness
<b>Hematologic</b>	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 independently<sup>41</sup> (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.<sup>42,43</sup> 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.<sup>44</sup>

## 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.<sup>45</sup>

## Reconstitution: Use Aseptic Technique

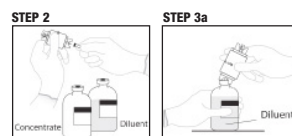
When reconstitution is performed aseptically **outside** of a sterile laminar air flow hood, administration should begin as soon as possible, but not more than 2 hours after reconstitution.

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.

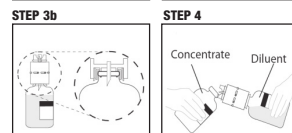
### A. 5% Solution

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

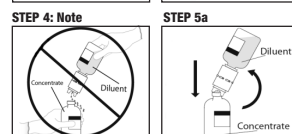
1. Remove bottle caps and clean stoppers with germicidal solution.
2. Remove spike cap from one end of the transfer device. Do not touch spike.
- 3a. Place diluent bottle on a flat surface. Use exposed end of transfer device to spike diluent bottle through center of the stopper.



- 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.

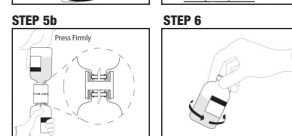


- While holding onto transfer device, remove remaining spike cover. Do not touch spike.
4. Hold diluent bottle with attached transfer device at an angle to the concentrate bottle to prevent spilling the diluent.



**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%	<b>Do not remove any diluent for reconstitution of 5% Solution</b>	
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.<sup>45</sup> 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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