PRODUCT MONOGRAPH

GAMMAGARD S/D, 0.5 g/vial, 2.5 g/vial, 5 g/vial & 10 g/vial

Immune Globulin Intravenous (Human) [IGIV],
Solvent/Detergent-Treated (Freeze-Dried Concentrate)

Replacement Therapy for Immunodeficiencies

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Freeze-Dried Concentrate 0.5 g/vial, 2.5 g/vial, 5 g/vial & 10 g/vial	None of the nonmedicinal ingredients are clinically relevant. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], is a sterile, freeze-dried preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. The product is manufactured by the Cohn-Oncley cold ethanol fractionation process followed by ultrafiltration and ion exchange chromatography. The manufacturing process includes treatment with an organic solvent/detergent mixture.

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.

This product is prepared from large pools of human plasma, which may contain the causative agents of hepatitis and viral diseases. (see WARNINGS AND PRECAUTIONS).

INDICATIONS AND CLINICAL USE

- **Primary Immunodeficiency Diseases**
  Immune Globulin Intravenous (Human) [IGIV], GAMMAGARD S/D, Solvent/Detergent-Treated is indicated for the treatment of primary immunodeficient states, such as:
  - congenital agammaglobulinemias
  - common variable immunodeficiency
  - Wiskott-Aldrich syndrome
  - severe combined immunodeficiencies[3,4]

- **B-cell Chronic Lymphocytic Leukemia (CLL)**
  IGIV, 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).

- **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 IGIV, GAMMAGARD S/D, should be considered.

Geriatrics and Pediatrics (>24 months of age):

No specific geriatric or pediatric studies were performed.

CONTRAINDICATIONS

Patients with IgA deficiency may experience severe hypersensitivity reactions or anaphylaxis in the setting of detectable IgA levels following infusion of GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated. The occurrence of severe hypersensitivity reactions or anaphylaxis should prompt consideration of an alternative therapy. GAMMAGARD S/D is contraindicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see WARNINGS AND PRECAUTIONS).

GAMMAGARD S/D should also be contraindicated in patients with a history of severe systemic or anaphylactic reactions to a human immune globulin preparation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, e.g., acute tubular necrosis, proximal tubular nephropathy, acute renal failure, osmotic nephrosis, and death.[25] Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, hypertension, 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 **Warnings and Precautions**, Impaired Renal Function and **Dosage and Administration** sections for important information intended to reduce the risk of acute renal failure.

*GAMMAGARD S/D does not contain sucrose.

General

GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated, is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infections agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens.

The risk of transmitting 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. The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for the nonenveloped viruses HAV and parovirus B19. (See PHARMACEUTICAL INFORMATION, Viral Inactivation).

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) and the variant Creutzfeldt-Jakob disease (vCJD) agents. 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 Corporation at 1-800-387-8399 (in Canada). The physician should discuss the risks and benefits

of this product with the patient.

The amount of sodium in the maximum daily dose of GAMMAGARD S/D may add materially to the recommended daily allowance of dietary sodium for patients on a low sodium diet. In these patients, the amount of sodium from the product should be calculated and taken into account when determining dietary sodium intake. GAMMAGARD S/D contains approximately 850 mg sodium per liter at a 5% concentration. A 70 kg patient receiving 1g/kg (1.4 L) would receive 1190 mg of sodium.

IGIV, GAMMAGARD S/D, should only be administered intravenously. Other routes of administration have not been evaluated.

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

Physicians should report adverse reactions or any disease conditions which may occur concomitantly with the administration of this product to the manufacturer.

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

Immune

Rarely, human normal immunoglobulin can induce an anaphylactic reaction with a fall in blood pressure, even in patients who had tolerated previous treatment with human normal immunoglobulin. Patients with antibodies to IgA or with IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated may be at increased risk of anaphylactic reaction. Anaphylaxis has been reported with the use of this product even though it contains low levels of IgA. IGIV, GAMMAGARD S/D, contains only trace amounts of IgA (≤2.2 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. GAMMAGARD S/D should be given with caution to patients with antibodies to IgA or IgA deficiency, that is a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated.[4,7] Patients who have had a severe hypersensitivity reaction should only receive intravenous immune globulin with utmost caution and in a setting where supportive care is a available for treating life-threatening reactions.

Impaired Renal Function

Assure that patients are not volume depleted prior to the initiation of the infusion of IGIV.

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. 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 amount of product infused per unit time by infusing GAMMAGARD S/D at a rate 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.

Haemolysis

GGSD, contains blood group antibodies that may act as hemolysins and induce in vivo coating of red blood cells (RBC) with immune globulin. This may cause a positive direct antiglobulin test [DAT (Coomb's test)]. Delayed hemolytic anemia can develop subsequent to GGSD therapy due to enhanced RBC sequestration; acute hemolysis, consistent with intravascular hemolysis, has been reported (see ADVERSE REACTIONS). IGIV recipients should be monitored for clinical signs and symptoms of haemolysis (see WARNINGS AND PRECAUTIONS: Monitoring and 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 including Gammagard S/D. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever, and typically occurs within 1-6 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 WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Thrombotic and Thromboembolic Events

There is clinical evidence of a possible association between GAMMAGARD S/D, Immune

Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated administration and the potential for the development of thrombotic and thromboembolic events, including myocardial infarction, cerebral vascular accident, deep vein thrombosis and pulmonary embolism. The exact cause of this is unknown; therefore, caution should be exercised in the prescribing and infusion of IGIV in patients with a history of and predisposing factors towards cardiovascular disease or thrombotic episodes, such as advanced age, restricted mobility, coagulation problems, gammopathies, diabetes, hypertension, cardiovascular problems or serious illness.[12-17, 18-23] Analysis of adverse events reports [22, 24] has indicated that a rapid rate of infusion may be a risk factor for vascular occlusive events.

For patients who are judged to be at risk for developing a thrombotic event the rate of infusion and percent of the solution concentrations should be targeted to the safety of the patient rather than convenience. Using a 5% concentration, the infusion rate should be initiated no faster than 0.5 mL/kg/hr and advanced slowly, only if well tolerated, to a maximum rate of 4 mL/kg/hr (<3.3 mg IgG/kg/min).

Aseptic Meningitis Syndrome

Aseptic meningitis syndrome (AMS) has been reported to occur in association with Immune Globulin Intravenous (Human) [IGIV], including Gammagard S/D treatment. Discontinuation of IGIV treatment may result in remission of AMS within several days. 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 cu.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.

Hyperproteinemia

Hyperproteinemia and increased serum viscosity may occur in patients received IGIV therapy.

Interference with Laboratory Tests

After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing, for example, Hepatitis A, Hepatitis B, measles, and varicella. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coombs test).

Information for Patients

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

Special Populations

The effects of GAMMAGARD S/D on fertility have not been established in controlled clinical trials.

Pregnancy and Lactation:

There are no adequate data from the use of GAMMAGARD S/D in pregnant or lactating women.

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

Maternally administered IGIV products have been shown to cross the placenta, increasingly during the third trimester. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing GAMMAGARD S/D.

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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.[26]

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

- acute renal failure
- acute tubular necrosis[27]
- proximal tubular nephropathy
- osmotic nephrosis[25, (see also 28-30)]

In general, reported adverse reactions to GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated 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 can occasionally occur. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug.

Primary Immunodeficiency Diseases

Adverse reactions were pooled from a clinical study of GAMMAGARD S/D in patients with primary immune deficiency disease and a phase 4 study assessing the acute and mid-term safety of GAMMAGARD S/D. The total number of subjects in these 2 studies was 84. Adverse reactions that occurred at a rate per infusion greater than or equal to 0.010 are shown in the table below.

GAMMAGARD S/D Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Rate per Infusion**
Nervous System Disorders	Headache	0.071
Vascular Disorders	Flushing	0.010
Gastrointestinal Disorders	Vomiting Nausea	0.010 0.033
General Disorders and Administration	Fatigue	0.025

Site Conditions	Chills Pyrexia	0.041 0.021

B-cell Chronic Lymphocytic Leukemia (CLL)

In the study of patients with B-cell Chronic Lymphocytic Leukemia, the incidence of adverse reactions associated with IGIV, GAMMAGARD infusions was approximately 1.3% while that associated with placebo (normal saline) infusions was 0.6%.[6]

Idiopathic Thrombocytopenic Purpura (ITP)

During the clinical study of IGIV, 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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Less common clinical trial adverse drug reactions in patients with primary immune deficiency disease are listed below.

Infections and Infestations: Influenza
Metabolism and Nutritional Disorders: Decreased Appetite
Psychiatric Disorders: Anxiety, Agitation
Nervous System Disorders: Lethargy
Eye Disorders: Vision blurred
Cardiac Disorders: Palpitations
Vascular Disorders: Blood Pressure Fluctuation
Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, Epistaxis
Gastrointestinal Disorders: Diarrhea, Abdominal pain upper, abdominal discomfort, Stomatitis
Skin And Subcutaneous Tissue Disorders: Pruritus, Urticaria, Cold sweat, Hyperhidrosis
Musculoskeletal And Connective Tissue Disorders: Back pain, Muscle spasms, Pain in extremity
General Disorders And Administration Site Conditions: Chest pain, Chest discomfort, Feeling abnormal, Feeling cold, Feeling hot, Influenza-like illness, Infusion site erythema, Infusion site extravasation, Infusion site pain, Malaise, Pain
Investigations: Blood pressure increased

Post-Market Adverse Drug Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported post-marketing. These adverse reactions are listed by System Order Class (SOC), then by Preferred MedDRA term in order of severity.

Infections and Infestations: Meningitis aseptic

Blood and Lymphatic System Disorders: Haemolysis, Anemia, , Thrombocytopenia, Lymphadenopathy

Immune System Disorders: Anaphylactic shock, Anaphylactic/anaphylactoid reaction, Hypersensitivity

Psychiatric Disorders: Restlessness

Nervous System Disorders: Cerebrovascular accident, Stroke, Transient ischemic attack, Convulsion, Migraine, Dizziness, Paresthesia, Syncope, Tremor

Eye Disorders: Retinal vein thrombosis, Visual impairment, Eye pain, Photophobia

Cardiac Disorders: Myocardial infarction, Cyanosis, Tachycardia, Bradycardia

Vascular Disorders: Arterial thrombosis, Vena cava thrombosis, Deep vein thrombosis, Thrombophlebitis, Hypotension, Hypertension, Pallor

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary embolism, Pulmonary edema, Hypoxia, Bronchospasm, Wheezing, Hyperventilation, Throat tightness, Cough

Gastrointestinal Disorders: Abdominal pain, Dyspepsia

Hepatobiliary Disorders: Hepatitis*

Skin and Subcutaneous Tissue Disorders: Angioedema, Dermatitis, Erythema, Rash

Musculoskeletal and Connective Tissue Disorders: Arthralgia, Myalgia

Renal and Urinary Disorders: Renal failure

General Disorders and Administration-Site Conditions: Infusion site reaction, Asthenia, EdemaChills

Investigations: Coombs direct test positive

*non-infectious hepatitis

DRUG INTERACTIONS

Overview

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

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, varicella and yellow fever for a period of at least six weeks and up to three months following infusion. Antibodies in immune globulin preparations may interfere with patient responses to live vaccines and the immunizing physician should be informed of recent therapy with IGIV so that appropriate precautions can be taken.

DOSAGE AND ADMINISTRATION

Dosing Considerations

When switching from the 5% solution to the 10% solution, the rate of the 10% solution should be initially reduced to keep the rate of IgG protein administration comparable. In many patients it is possible to gradually increase the rate of the 10% solution up to 8 mL/kg/hr. The rate of administration is individualized based on the tolerability of the patient.

In patients at risk for acute renal failure or thromboembolic adverse reactions, GAMMAGARD S/D should not be administered at the maximum allowable rate of infusion.

In general, it is recommended that patients beginning therapy with GAMMAGARD S/D or switching from one IGIV brand 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.

Recommended Dose and Dosage Adjustment

Primary Immunodeficiency Diseases

For patients with primary immunodeficiencies, monthly doses of at least 100 mg/kg are recommended. Initially, patients may receive 200-400 mg/kg. As there are significant differences in the half-life of IgG among patients with primary immunodeficiencies, 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 has not been established.

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.

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, 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.[31]

Missed Dose

Give product at the earliest available opportunity.

Administration

Reconstitution:

The reconstituted product may be stored in either the original vial or pooled into VIAFLEX bags. When reconstitution is performed aseptically in a sterile environment, the following storage guidelines are recommended: 24 hours at 5ºC; or 12 hours at 25ºC; or 12 hours at 25ºC followed by 12 hours at 5ºC.

Reconstitution: Use Aseptic Technique

A. 5% Solution

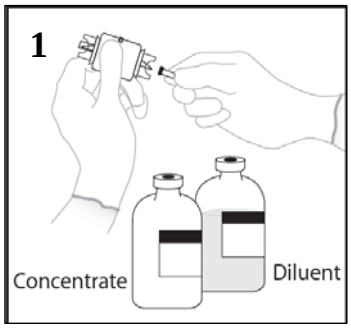
1. **Note: Reconstitute immediately before use.**
2. If refrigerated, warm the Sterile Water for Injection, USP (diluent) and GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated (freeze-dried concentrate), to room temperature.
3. Remove caps from concentrate and diluent vials to expose central portion of rubber stoppers.
4. Cleanse stoppers with germicidal solution and allow to dry.

For 0.5 g vials only:

5. Remove protective covering from one end of the double-ended needle and insert exposed needle through diluent stopper at its **center**.
6. Remove protective covering from other end of double-ended needle. Invert diluent vial over upright concentrate vial, then rapidly insert free end of the needle through the concentrate vial stopper at its **center**.
7. The vacuum in the concentrate vial will draw in the diluent. When diluent transfer is complete, remove empty diluent vial from needle and then needle from concentrate vial. Discard needle after single use.
8. Thoroughly wet the dried material by tilting or inverting and gently rotating the vial. **Do not shake. Avoid foaming.**
9. Repeat gentle rotation as long as undissolved product is observed.

For 2.5 g, 5 g & 10 g vials:

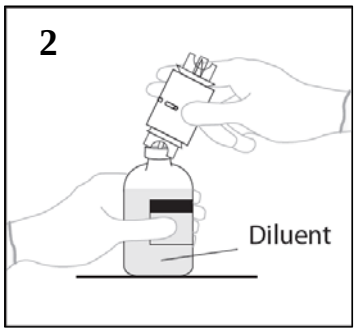
5. Remove spike cap from one end of transfer device. Do not touch spike (Fig 1).

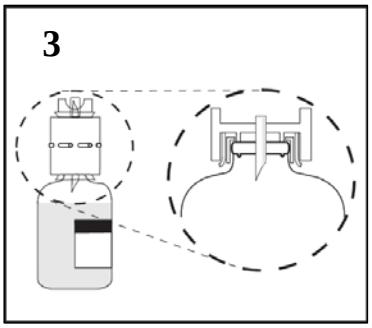


6a. Place diluent vial on flat surface. Use exposed end of transfer device to spike diluent vial through centre of the stopper (Fig 2).

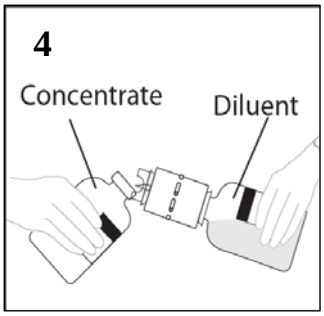
CAUTION: Failure to insert spike into centre of the stopper may result in dislodging of the stopper

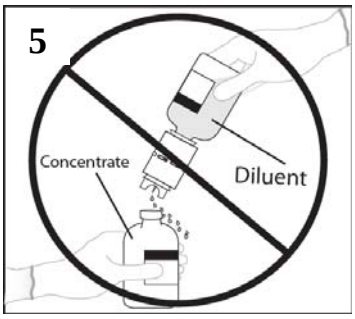
6b. Ensure the collar collapses fully into the device by pushing down on the transfer device firmly (Fig 3). While holding onto transfer device, remove remaining spike cover. Do not touch spike





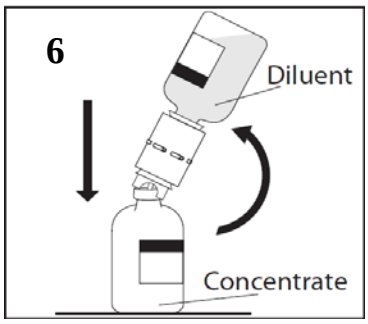
7. Hold diluent vial with attached transfer device at an angle to the concentrate vial to prevent spilling the diluent (Fig 4).
Note: Do not hold diluent vial upside down, for this can lead to diluent spillage (Fig 5)**.**

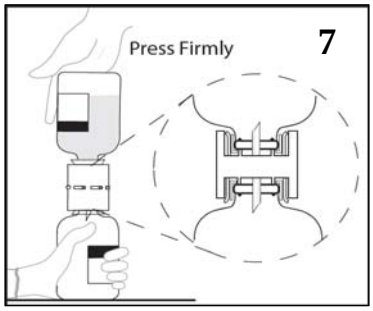




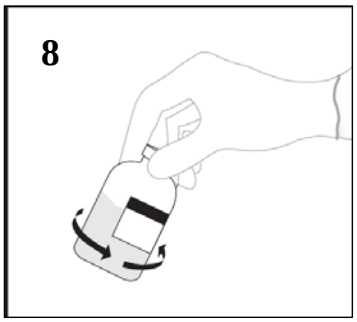
8. Spike concentrate vial through centre of the stopper while **quickly inverting the diluent vial** to minimize spilling out diluent (Fig 6).
CAUTION: Failure to insert the spike into the centre of the stopper may result in dislodging of the stopper and loss of vacuum.

9. Ensure that stopper collapses fully into the device by pushing down on the diluent vial firmly (Fig 7).





10. After transfer of diluent is complete, remove transfer device and empty diluent vial. Immediately swirl the concentrate vial gently to thoroughly mix contents (Fig 8). Discard transfer device after single use per local guidelines.
CAUTION: Do not shake. Avoid foaming.



B. 10% Solution

Follow steps 1-4 as previously described in **A**.

For 0.5 g vials only:

5. To prepare a 10% solution, reconstitute with the appropriate volume of diluent by using a sterile hypodermic syringe and needle. Table 1 indicates the volume of diluent required for 5% or 10% concentration. Using aseptic technique, draw required volume into a sterile hypodermic syringe and needle. The diluent is then injected into the concentrate vial.
6. Discard any unused diluent after single use.
7. Thoroughly wet the dried material by tilting or inverting and gently rotating the vial. **Do not shake. Avoid foaming.**
8. Repeat gentle rotation as long as undissolved product is observed.

For 2.5 g, 5 g & 10 g vials:

5. To prepare a 10% solution, it is necessary to remove half of the volume of diluent. Table 1 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 necessary volume of diluent using a sterile hypodermic needle and syringe. Discard the filled syringe into a suitable puncture proof container.

6. Using the residual diluent in the diluent vial, follow steps 5 – 10 as previously described in **A**.

TABLE 1

Required Diluent Volume to be Removed

Concentration	0.5 g/vial	2.5 g/vial	5 g/vial	10 g/vial
5%	**Do not remove any diluent for reconstitution of 5% solution**			
10%	**5 mL**	**25 mL**	**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. 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.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMMAGARD S/D at a rate 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.

For patients who are judged to be at risk for developing a thrombotic event the rate of infusion and percent of the solution concentrations should be targeted to the safety of the patient rather than convenience. Using a 5% concentration, the infusion rate should be initiated no faster than 0.5 mL/kg/hr and advanced slowly, only if well tolerated, to a maximum rate of 4 mL/kg/hr (<3.3 mg IgG/kg/min).

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 that is too rapid may cause headaches, flushing and changes in pulse rate and blood pressure. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. The infusion may then be resumed at a rate that does not result in recurrence of the symptoms.

Adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time, or when they switch from another IGIV brand, or when there has been a long interval since the previous infusion (see ADVERSE REACTIONS).

Administration:

FOR INTRAVENOUS USE ONLY.

IGIV, GAMMAGARD S/D, should be administered as soon after reconstitution as possible.

The reconstituted material should be at room temperature during administration.

GGSD should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Before reconstitution the powder should be white or very faint yellow powder/cake that is substantially free of foreign visible particles. After reconstitution, only clear or slightly opalescent and colourless or pale yellow solutions are to be administered

For 0.5 g vials only:

Intravenous Syringe Injection

1. Attach filter needle to a disposable syringe and draw back plunger to admit air into syringe.
2. Insert needle into reconstituted GAMMAGARD S/D.
3. Inject air into vial and then withdraw the reconstituted material into the syringe.
4. Remove and discard the filter needle from the syringe; attach a suitable needle and inject intravenously as instructed under Rate of Administration.

For 2.5 g, 5 g & 10 g vials:

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

OVERDOSAGE

No overdosage has been reported for GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent - Treated, Solvent/Detergent-Treated.

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

For management of a suspected drug overdose, contact your regional poison Control Center

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Immunoglobulins are the main effector molecules of the humoral immune response. They have two separable functions: one is to bind specifically to the antigen of the pathogen that elicited the immune response via their antigen-binding region; the other is to engage the effector functions of the immune system that will dispose of the antigen via their constant Fc region.

Immunoglobulins can protect from pathogens or their toxic products in three distinct ways:

- By binding of immunoglobulin to the antigen, its access to cells is blocked, i.e. the antigen is neutralized.
- When pathogens or foreign particles are coated by immunoglobulins, a process known as opsonization, the Fc portion of the antibody engages specific receptors on phagocytic cells resulting in the removal and destruction of the pathogen.
- The Fc portion of antigen-antibody complexes can activate complement, which enhances engulfment of pathogens by phagocytes or direct damage of certain bacteria.

Pharmacodynamics

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

Pharmacokinetics

Absorption:

Peak levels of IgG are reached immediately after infusion of IGIV, GAMMAGARD S/D.

Distribution and Metabolism:

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.[1] As a class, IgG survives longer *in vivo* than other serum proteins.[1,2]

Excretion:

Studies show that the half life of IGIV, GAMMAGARD S/D, is approximately 37.7 ± 15 days.[11] Previous studies reported IgG half-life values of 21 to 25 days.[1-3] 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.[1-4]

Special Populations and Conditions

Pharmacokinetic information was not established in distinct studies for special populations and conditions.

STORAGE AND STABILITY

IGIV, 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 vial from breaking. Do not use after the expiration date. Any unused solution must be discarded due to the risk of bacterial contamination. Store out of reach of children.

Reconstituted Solutions
IGIV, GAMMAGARD S/D, should be administered intravenously after reconstitution with the appropriate volume of Water for Injection, USP (diluent) provided in each package. Refer to Table 1: Required Diluent Volume under DOSAGE AND ADMINISTRATION for the quantity of diluent required to produce both 5% and 10% concentrations of GAMMAGARD S/D.

The reconstituted product may be stored in either the original vial or pooled into VIAFLEX bags. When reconstitution is performed aseptically in a sterile environment, the following storage guidelines are recommended: 24 hours at 5ºC; or 12 hours at 25ºC; or 12 hours at 25ºC followed by 12 hours at 5ºC.

Parenteral Solutions
GAMMAGARD S/D preparations should not be mixed with other pharmaceutical products. Administer separately from other medications.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GAMMAGARD S/D, Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent – Treated is available in 0.5 g/vial, 2.5 g/vial, 5 g/vial and 10 g/vial sizes of freeze-dried concentrate The 2.5g/vial, 5g/vial and 10g/vial sizes are packaged with Sterile Water for Injection, USP (diluent), one transfer device, one administration set and directions for use. The

0.5 g/vial single dose pack size of freeze-dried concentrate, is packaged with Sterile Water for Injection, USP (diluent), a double-ended needle, a filter spike, and directions for use.

The volume of diluent provided with each IGIV, GAMMAGARD S/D package size is as follows:

Vial Size-IGIV, GAMMAGARD S/D	Vial Size-Sterile Water for Injection, USP
0.5 g	10 mL
2.5 g	50 mL
5 g	96 mL
10 g	192 mL

The freeze-dried concentrate and diluent are provided in Type 1 USP clear glass, single dose vials each with a rubber stopper and an aluminum cap with a twist-off center.

IGIV, GAMMAGARD S/D should be administered intravenously after reconstitution with the appropriate volume of Sterile Water for Injection, USP provided with each package.

Composition

IGIV, GAMMAGARD S/D, may be reconstituted with diluent (Water for Injection, USP) to a 5% (50 mg/mL) solution or a 10% (100 mg/mL) solution of protein 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 dextrose

2 mg/mL polyethylene glycol (PEG)

1 µg/mL tri(n-butyl) phosphate

1 µg/mL octoxynol 9

100 µg/mL polysorbate 80

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 the DOSAGE AND ADMINISTRATION section. In this case, the stabilizing agents and other components will be present at double the concentrations given for the 5% solution.

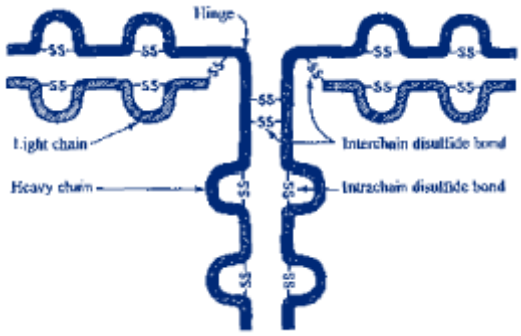
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Human normal immunoglobulin G (IgG)

Structure of the IgG Molecule:



The IgG antibody molecule is made up of four polypeptide chains held together by disulfide bonds. Two of the chains are small, with molecular weights of 22,000, and are termed light chains. The other two, with molecular weights of 55,000 are called heavy chains. Each immunoglobulin molecule has two identical heavy chains and two identical light chains.

Product Characteristics

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-Oncley cold ethanol fractionation process followed by ultrafiltration and ion exchange chromatography. The manufacturing process includes treatment with an organic solvent/detergent mixture,[9,10] composed of tri(n-butyl) phosphate, octoxynol 9 and polysorbate 80.[11]

The manufacturing process for IGIV, GAMMAGARD S/D, isolates IgG without additional chemical or enzymatic modification and the Fc portion is maintained intact. IGIV, 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.[11] IGIV, GAMMAGARD S/D, contains only trace amounts of IgA (≤2.2 μg/mL in a 5% solution). IgM is also present in trace amounts (≤10 mg/dL in a 5% solution).

Viral Inactivation

The GAMMAGARD S/D manufacturing process provides a significant viral reduction in *in vitro* studies.[11] These studies, summarized in Table 2, demonstrate virus clearance during GAMMAGARD S/D manufacturing. These reductions are achieved through a combination of process chemistry, partitioning and/or inactivation during cold ethanol fractionation and the solvent/detergent treatment.[11]

Reduction factors (RFs) from the most recent and/or most comprehensive studies were used for this summary table. Only RFs for steps based on *different* mechanisms of virus removal[a] / inactivation were used for calculation of the overall reduction factor (ORF). RFs used for calculation of the ORF are marked in bold. Study report numbers are provided in footnotes.

***In Vitro* Virus Clearance During IGIV, GAMMAGARD S/D, Manufacturing**							
Process Step Evaluated	**Reduction Factor (log_{10})**						
	Lipid Enveloped Viruses				**Non-Enveloped Viruses**		
	HIV	**BVDV**	**WNV**	**PRV**	**HAV**	**B19V**	**Parvo Model *(PPV / MMV)***
Step 1: From Cryo-Poor Plasma to Fraction I+II+III Precipitate	5.6 [b]	0.6 [c]	ND	1.0 [d]	0.5 [e]	ND	0.2 [f]
Step 2&3 combined: From Resuspended Precipitate A to Cuno 70 Filtrate	**>5.8** [g]	**2.7** g	**>5.8** g	**>5.7** g	**4.3** [h]	**>4.1** [i]	**>4.9 (PPV)**[j] **5.3 (MMV)** g
Step 4: S/D Treatment	**>3.7** [k]	**>8.4** [l]	**>6.0** [m]	**>4.1** [n]	NA	NA	NA
Overall log_{10} Reduction Factor (ORF)	**>9.5**	**>11.1**	**>11.8**	**>9.8**	**4.3**	**>4.1**	**>4.9 / 5.3**

ND not done; NA not applicable (SD treatment not effective against non-enveloped viruses); HIV Human Immunodeficiency virus, BVDV Bovine viral diarrhea virus; WNV West Nile virus; PRV Pseudorabies virus, HAV Hepatitis A virus; B19V Human Parvovirus B19, PPV Porcine parvovirus; MMV Mice minute virus

[a] Therefore, reduction factors for the steps 1 and (2&3 combined) were not added *together* for the ORF, as the mechanism of virus clearance is the same for all these steps (virus clearance by precipitation)
[b] Report 96002-CMC-017
[c] Report 96002-CMC-015
[d] Report 96002-CMC-012
[e] Report 96002-CMC-018
[f] Report 96002-CMC-016 (PPV Data)
[g] Report reg642e
[h] Mean of 4.1 (report 94016-CMC-062) and >4.5 (reg642e)
[i] Report 94016-CMC-063
[j] Report 94016-CMC-066
[k] Report 94016-CMC-048
[l] Report reg644e (for a more comprehensive investigation of the SD treatment, a high-volume assay was used for detection of BVDV)
[m] Report preg007e (investigational study) + Amendment AD1_PE0102
[n] Report 94016-CMC-046

Plasma Screening

Each donation is tested for infectious disease markers for Human Immunodeficiency Virus, (HIV), Hepatitis C Virus (HCV), Hepatitis B Surface Antigen (HBsAg), as well as HIV and HCV by Nucleic Acid Technology (NAT).

The criteria for release of each single plasma donation for further manufacturing are therefore as follows:

- HIV- 1/2 antibody — non- reactive
- HBsAg — non-reactive
- HCV antibody — non-reactive
- HIV-1 NAT[1] — non-reactive
- HCV NAT[1] — non-reactive

[1] Tested in mini-pool format

Tests carried out on the Manufacturing Plasma Pools

Each manufacturing plasma pool prepared for the manufacture of plasma derivatives is also tested for HBsAg and HIV-1/2 antibodies, as well as by NAT. Only plasma pools negative by NAT for HIV, HBV, HCV, HAV and not exceeding 10^4 IU PVB19 DNA/ml are released for further manufacture.

System to Trace the Path of Any Donation

Baxter has procedures in place which clearly outline how each plasma unit can be traced to the individual donor from collection at the collection center through finished product and vice versa.

CLINICAL TRIALS

The indication for the treatment of primary immunodeficient states was supported by a clinical trial of 17 patients with primary immunodeficiency who received a total of 341 infusions. IGIV, 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).

In a study of 81 patients with B-cell Chronic Lymphocytic Leukemia (CLL), 41 of whom were treated with IGIV, GAMMAGARD, bacterial infections were significantly reduced in the treatment group.5,6 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.

The efficacy of IGIV, GAMMAGARD in the treatment of Idiopathic Thrombocytopenic Purpura (ITP) 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^3 following the administration of IGIV, GAMMAGARD. Ten of the 16 patients (62.5%) exhibited a significant rise to greater than 80,000 platelets/mm^3. 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^3 occurred after a single 1 g/kg infusion of IGIV, 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^3. 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.

Safety data from two studies representing a total of 363 infusions are available at this time. The first study was a pharmacokinetic/acute safety trial comparing GAMMAGARD and GAMMAGARD S/D. The second open label study is evaluating viral safety of lyophilized IGIV S/D.

Fifteen primary immunodeficient patients, ten with previous exposure to IGIV and/or Immune Serum Globulin (previously treated) and five with no previous exposure (previously untreated) participated in the pharmacokinetic/acute safety trial. The five previously untreated patients have completed the pharmacokinetic study were subsequently enrolled in the open label long term viral safety study of GAMMAGARD S/D, together with 26 additional previously untreated patients. The enrollment of this study is now closed and these patients are in active follow-up.

In the pharmacokinetic/acute safety trial, a total of 5 of 28 infusions (17.9%) in previously treated patients were associated with adverse reactions. Of the 28 infusions, ten received untreated GAMMAGARD with three adverse reactions (30%) reported. Eighteen received GAMMAGARD S/D with two adverse reactions (11.1%) reported. All five of these reported events were described as systemic symptoms, e.g., flushing, chills, nausea, or abdominal pain. None of the previously treated patients reported local pain or irritation at the intravenous needle site. Neither the incidence nor type of adverse reactions reported was significantly different following infusion of GAMMAGARD or GAMMAGARD S/D.

No serious or life threatening adverse events were reported in either study. Among the 31 previously untreated patients in the viral safety trial, 37 adverse events have been reported in

association with 325 infusions (11.4%). All adverse reactions were systemic in nature and there were no reports of local pain or irritation at the intravenous needle site. Excluding the two study subjects in whom the vast majority of adverse events were reported, the overall incidence of adverse reactions for GAMMAGARD S/D (6%) is similar to the historical experience with the formerly licensed GAMMAGARD.

To date, there has been no seroconversion to anti-HIV-1 or HBsAg positivity in any study subject. Evaluation of serial liver transaminase levels reveals no evidence of hepatic inflammation in any study subject during the post-infusion observation period. Borderline, non-recurring elevations in serum AST have been noted on 5 occasions in 4 study subjects with levels ranging from 51 to 73.5 IU/L. These always occurred in association with concomitantly measured normal ALT levels.

DETAILED PHARMACOLOGY

GAMMAGARD, Immune Globulin Intravenous (Human) [IGIV] has been well-tolerated for years, and Immune Globulin Intravenous (Human) [IGIV], Solvent/Detergent-Treated, GAMMAGARD S/D (IGIV S/D) is the same product with additional anti-viral assurance. As such, a testing program was designed primarily to demonstrate that solvent/detergent treatment will neither alter the functional activity of the active ingredient nor decrease its circulating serum half-life.

In vitro studies performed to compare IGIV S/D with IGIV were designed to evaluate the Fab and Fc portions of the immunoglobulin molecules. Opsonophagocytosis of microorganisms is among the most important functional activities of an antibody developed for treatment of infectious disease, making these studies highly relevant. Opsonization experiments examine the activity of both the Fab and Fc portions of the molecule. Numerous studies have been performed to evaluate the opsonic capability of immune globulin products. Comparative evaluation of the functional activity of GAMMAGARD and GAMMAGARD S/D, showed that the two products demonstrate antibody function that is virtually identical.

After efficacy evaluation of the treated IGIV S/D and untreated IGIV products showed functional similarity, a pharmacokinetic study was performed to ensure that solvent/detergent treatment would not shorten the serum half-life and accelerate clearance of the circulating antibody. Comparative clearance of IGIV S/D and IGIV was evaluated in male Sprague-Dawley rats following administration of a single bolus injection. Six formulated IGIV S/D lots, were compared with six formulated lots of untreated IGIV. Intravenous immune globulin is administered clinically as a slow infusion, but the study material had to be administered as a bolus injection to achieve an immediate maximum concentration of 100 mg/mL. This

concentration is twice that recommended by the manufacturer, but it was chosen to minimize the injected fluid volume and still administer the desired IgG concentration. There was no significant difference in the clearance of IGIV S/D from the plasma of rats.

The required specifications for immune globulin preparations that may be safely infused intravenously are all met by GAMMAGARD S/D in that this therapy is prepared from a large donor plasma pool resulting in a very broad range of antibodies, consistency in antibody titers, normal distribution of IgG subclasses and no more than two percent of IgG aggregates. In addition, GAMMAGARD S/D consists of intact IgG with functional Fc component which maximizes the efficacy of that treatment and also a very low IgA level (≤2.2 μg/mL in a 5% solution) which contributes substantially to the safety of this therapy.

Extensive pharmacokinetic analysis of GAMMAGARD has been carried out in normal individuals, persons with primary immunodeficiencies, persons with secondary (acquired) immunodeficiencies such as chronic lymphocytic leukemia, and in low birthweight neonates. These studies have all shown that the pharmacokinetic characteristics of the therapy are equivalent to natural IgG and its subclasses, as well as similar to that of other commercial IGIV preparations. In addition, these similarities extend to specific titers of antibodies to cytomegalovirus and *Streptococcus pneumoniae*. The efficacy of GAMMAGARD as a modulating agent of immunity has been extensively evaluated in a variety of disease processes.

MICROBIOLOGY

Not Applicable

TOXICOLOGY

Preclinical

Since immunoglobulins are naturally occurring substances, toxicology studies focused on potential toxicity of the solvent/detergent used for viral inactivation. To determine the effect of repeated infusions of solvent/detergent-treated immune globulin, acute toxicity was evaluated in primates at concentrations of one and five times the expected maximum dose. Repeat dose toxicity of three different concentrations of the solvent/detergent mixture, administered every three days over a six month period, was evaluated in rats. There were no product-related abnormalities observed in any of the test animals.

Red-tinged urine, possibly due to red cell haemolysis, caused by intravenous administration of relatively large doses of Triton X-100, was observed in rats. Based on the Immune Globulin Intravenous (Human) [IGIV], GAMMAGARD S/D, Solvent/Detergent-Treated maximum product specification of one part per million of Triton X-100, the haemolytic test dose administered was 1,000 times the maximum permitted in the manufactured product. Because the *in vivo* concentration of Triton X-100 exceeded the *in vitro* haemolytic dose in rat blood, the observation of red-tinged urine is explicable. The residual amount of 0.0001% Triton X-100 should not cause haemolysis when administered in a clinical situation because the concentration of Triton X-100 would be negligible.

Extensive literature exists which deals with the toxicity of the individual components of the solvent/detergent mixture. The nonionic surfactants, Triton X-100 and Tween® 80 are primarily used in cosmetic, food and pharmaceutical formulations as emulsifiers, wetting agents, solubilizers and stabilizers. Triton X-100 is available as an over-the-counter vaginal spermicide, as well as in hair and skin care products at concentrations ranging from 0.1 to 50%. Tween® 80, found in cosmetic products at concentrations ranging between 0.1 and 25%, is also an inactive ingredient in pharmaceutical products approved for injection, oral and topical use. In addition, it has been approved for direct use as a synthetic flavoring, emulsifier, solubilizer, etc. in foods. In biological research, Tween® 80 has been used in membrane protein extraction and viral inactivation. These approved uses imply that there is no residual solvent/detergent toxicity.

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33. Baxter, Gammagard and Viaflex are trademarks of Baxter International, Inc., and are registered in the U.S. Patent and Trademark Office.

34. Baxter, Company Core Safety Information, GAMMAGARD S/D, Immune Globulin Intravenous Human (IGIV). 2010 October.

PART III: CONSUMER INFORMATION

GAMMAGARD S/D

Immune Globulin Intravenous (Human), [IGIV] 10%

This leaflet is part III of a three-part "Product Monograph" published when GAMMAGARD S/D was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GAMMAGARD S/D. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

GAMMAGARD S/D is used for the following:

Replacement therapy in

- **Primary immunodeficiency syndromes (PID) Including:**
  - Congenital agammaglobulinaemia and hypogammaglobulinaemia
  - Common variable immunodeficiency
  - Wiskott Aldrich syndrome
  - Severe combined immunodeficiency
- **B-cell Chronic Lymphocytic Leukemia (CLL)**
- **Idiopathic thrombocytopenic purpura (ITP)**

What it does:

GAMMAGARD S/D belongs to a class of medicines called immunoglobulins. These medicines contain human antibodies, which are also present in your blood. Antibodies help your body to fight infections. Immunoglobulins are used in patients who do not have enough antibodies in their blood and tend to get frequent infections. They can also be used in patients who need additional antibodies for the treatment of certain inflammatory disorders.

When it should not be used:

GAMMAGARD S/D must not be used

- If you are hypersensitive (allergic) to immunoglobulins or to the other ingredient of GAMMAGARD S/D.

- If you have an immunoglobulin A deficiency (lack of IgA antibodies), you may have antibodies against immunoglobulin A in your blood. Since GAMMAGARD S/D contains small amounts of immunoglobulin A (≤2.2 μg/mL in a 5% solution), you might develop an allergic reaction.

What the medicinal ingredient is:

The active substance is human normal immunoglobulin.

GAMMAGARD S/D may be reconstituted with diluent (Water for Injection, USP) to a 5% (50 mg/mL) solution or a 10% (100 mg/mL) solution of protein of which at least 90% is gamma globulin.

What the important nonmedicinal ingredients are:

The other ingredients are:

- Albumin (Human)
- Glycine
- Dextrose
- Polyethylene glycol (PEG)
- Tri(n-butyl) phosphate
- Octoxynol 9

Polysorbate 80

What dosage forms it comes in:

GAMMAGARD S/D is available in 0.5 g/vial, 2.5 g/vial, 5 g/vial and 10 g/vial size vials of freeze-dried concentrate, which is packaged with Sterile Water for Injection, USP (diluent), a transfer device, and an administration set.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Immune Globulin Intravenous (IGIV) products have been reported to cause:

- Disease of the kidneys
- Failure of the kidneys
- Damage to the tubes inside of the kidneys
- Death

People with an increased risk of kidney damage include those with any degree of existing kidney disease, diabetes, age greater than 65, dehydrated, have an overwhelming infection, have abnormal proteins in their blood, or patients receiving drugs known to damage the kidneys. Especially in these people, IGIV products should be administered at the lowest possible concentration and as slowly as is practical. While these reports of kidney disease and failure of the kidneys have been associated with the use of many of the licensed IGIV products, those containin sucrose produced more kidney problems than expected.

Gammagard S/D does NOT contain sucrose.

You should discuss the risks and benefits of this product with your physician.

INTERACTIONS WITH THIS MEDICATION

- Please inform your doctor if you are taking, or have recently taken any other medicines, even those not prescribed, or if you have received a vaccination during the last six weeks.
- Infusion of immunoglobulins like GAMMAGARD S/D may impair the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox vaccines. Therefore, after receiving immunoglobulins you may have to wait up to 3 months before receiving your live-attenuated vaccine. You may have to wait for up to 1 year after receiving immunoglobulins before you receive your measles vaccine.
- GAMMAGARD S/D contains a wide variety of different antibodies, some of which can affect blood tests. If you have a blood test after receiving GAMMAGARD S/D, please inform the person taking your blood or your doctor about your infusion.

PROPER USE OF THIS MEDICATION

Usual dose:

GAMMAGARD S/D is intended for intravenous administration (infusion into a vein). It is given to you by your doctor. Dosage will vary depending on your condition and your bodyweight.

At the beginning of your infusion you will receive GAMMAGARD S/D at a slow rate (0.5 mL/kg of bodyweight/hour). Depending on how comfortable you are your doctor may then gradually increase the infusion rate to a maximum of 8 mL/kg of bodyweight/hour.

Overdose:

If you receive more GAMMAGARD S/D than you should, your blood may become too thick (hyperviscose). This could particularly happen when you are a patient at risk, e.g. an elderly patient or a patient having problems with your kidneys.

In case of drug overdose, contact the regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Take GAMMAGARD S/D at the earliest available opportunity.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, GAMMAGARD S/D can have side effects. However, possible side effects may be reduced by slowing the infusion rate.

- General reactions such as chills, headaches, fever, vomiting, allergic reactions, nausea, joint pain, low blood pressure and moderate lower back pain have been experienced occasionally.
- Rarely, cases of a sudden fall in blood pressure were observed, and in isolated cases allergic reactions (anaphylactic shock), even in patients who have shown no reactions to previous infusions. Symptoms for an immediate allergic reaction are bronchitis or asthma, flu-like symptoms, pink eye, generalized rash, skin oedema (angiooedema), dizziness and collapse.
- Cases of temporary meningitis (reversible aseptic meningitis), isolated cases of temporary decrease of red blood cells (reversible haemolytic anaemia/haemolysis) and rare cases of eczema-like symptoms (transient cutaneous reactions) have been observed with

immunoglobulin products.

- An increase in blood creatinine content and kidney failure has also been observed.
- Very rarely, cases of blood clot formation in the veins (thromboembolic reactions) resulting in cardiac infarction, stroke, lung embolism, and deep vein thrombosis have been reported.
- If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Anaphylactic Shock		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common				
Uncommon				
Rare	✓		✓	✓
Very rare				
Renal insufficiency		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common				
Uncommon				
Rare	✓		✓	✓
Very rare				
Reversible aseptic meningitis		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common				
Uncommon				
Rare	✓		✓	✓
Very rare				
Thromboembolic events		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common				
Uncommon				
Rare	✓		✓	✓
Very rare				

This is not a complete list of side effects. For any unexpected effects while taking GAMMAGARD S/D contact your doctor or pharmacist.

HOW TO STORE IT

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 vial from breaking. Do not use after the expiration date. Any unused solution must be discarded due to the risk of bacterial contamination. Store out of reach of children.

Do not use after the expiry date stated on the label.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

    Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.baxter.com

Or by calling the sponsor, Baxter Corporation at: 1-800-387-8399

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