

GAMMAGARD LIQUID

[Immune Globulin Intravenous (Human)] 10%

Initial U.S. Approval: 2005

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMMAGARD LIQUID safely and effectively. See full prescribing information for GAMMAGARD LIQUID.

GAMMAGARD LIQUID, Immune Globulin Intravenous (Human), 10% Solution

Warning

See full prescribing information for complete boxed warning

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products that contain sucrose. GAMMAGARD LIQUID does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer GAMMAGARD LIQUID at the minimum rate of infusion practicable.

INDICATIONS AND USAGE

GAMMAGARD LIQUID is an Immune Globulin Intravenous (Human), 10% liquid indicated for the treatment of primary immunodeficiency (PI) (1.1).

DOSAGE AND ADMINISTRATION

Intravenous Use Only

Dose	Initial Infusion Rate	Increased Infusion Rate
300 to 600 mg/kg every 3 to 4 weeks	0.5 mL/kg/hr (0.8 mg/kg/min)	every 30 minutes (if tolerated) to a maximum rate of 5.0 mL/kg/hr (8 mg/kg/min)

- Adjust the dosage based on clinical response (2.2).
- Individualize rates for each patient (2.3).
- It is recommended that patients beginning therapy with GAMMAGARD LIQUID or switching from another IGIV product be started at the lower rates and then advanced to the maximal rate (2.3).
- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMMAGARD LIQUID if renal function deteriorates (2.3).
- For patients at risk of renal dysfunction or thrombotic events, administer GAMMAGARD LIQUID at the minimum infusion rate practicable (2.3).

DOSAGE FORMS AND STRENGTHS

GAMMAGARD LIQUID is a liquid solution containing 10% IgG (100 mg/mL) (3).

CONTRAINDICATIONS

- History of anaphylactic or severe systemic reactions to Immune Globulin (Human) (4).
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4).

WARNINGS and PRECAUTIONS

- IgA deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reaction (5.1).
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure (5.2).
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving GAMMAGARD LIQUID therapy (5.3).
- Thromboembolic events may occur. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk for hyperviscosity (5.4).
- Aseptic Meningitis Syndrome (AMS) has been reported in patients receiving GAMMAGARD LIQUID therapy (5.5).
- Hemolytic anemia can develop subsequent to GAMMAGARD LIQUID therapy. Monitor patients for clinical signs and symptoms of hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI) (5.7).
- GAMMAGARD LIQUID is made from human plasma and may contain infectious agents, e.g., viruses and theoretically, Creutzfeldt-Jacob disease (CJD) agent (5.8).

ADVERSE REACTIONS

The most common adverse reactions observed in ≥ 5 percent of the subjects were headache, pyrexia, fatigue, rigors, nausea, chills, dizziness, vomiting, migraine headache, pain in extremity, urticaria and cough (6.1).

Severe adverse reaction that occurred in the clinical trial were two episodes of aseptic meningitis in a single subject (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune responses to live virus vaccines, such as measles, mumps, and rubella (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly indicated (8.1).
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse GAMMAGARD LIQUID at the minimum infusion rate practicable (8.5).

See Section 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE	5 WARNINGS AND PRECAUTIONS	6 ADVERSE REACTIONS	12 CLINICAL PHARMACOLOGY
1 INDICATIONS AND USAGE	5.1 Hypersensitivity	6.1 Clinical Trials Experience	12.1 Mechanism of Action
2 DOSAGE AND ADMINISTRATION	5.2 Renal Dysfunction/Failure	6.2 Postmarketing Experience	12.3 Pharmacokinetics
2.1 Preparation and Handling	5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia	7 DRUG INTERACTIONS	14 CLINICAL STUDIES
2.2 Dose	5.4 Thromboembolic Event	8 USE IN SPECIFIC POPULATIONS	15 REFERENCES
2.3 Administration	5.5 Aseptic Meningitis Syndrome (AMS)	8.1 Pregnancy	16 HOW SUPPLIED/STORAGE AND HANDLING
3 DOSAGE FORMS AND STRENGTHS	5.6 Hemolysis	8.3 Nursing Mothers	17 PATIENT COUNSELING INFORMATION
4 CONTRAINDICATIONS	5.7 Transfusion-Related Acute Lung Injury (TRALI)	8.4 Pediatric Use	* Sections or subsections omitted from the full prescribing information are not listed.
	5.8 Transmissible Infectious Agents	8.5 Geriatric Use	
	5.9 Monitoring: Laboratory Tests	10 OVERDOSAGE	
	5.10 Interference with Laboratory Tests	11 DESCRIPTION	

Revised: 12/2010

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FULL PRESCRIBING INFORMATION**WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

- Use of Immune Globulin Intravenous (Human) (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those receiving known nephrotoxic drugs. GAMMAGARD LIQUID does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer GAMMAGARD LIQUID at the minimum infusion rate practicable.

1. INDICATION AND USAGE

GAMMAGARD LIQUID is indicated for the treatment of patients with primary immunodeficiency (PI) associated with defects in humoral immunity. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.^{1,2}

2. DOSAGE AND ADMINISTRATION**Intravenous Use Only****2.1 Preparation and Handling**

- GAMMAGARD LIQUID is a clear or slightly opalescent, colorless or pale yellow solution. Inspect the drug product visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy, turbid, or if it contains particulates.
- Allow refrigerated product to come to room temperature before use. DO NOT MICROWAVE.
- Do not shake.
- Do not mix with other products.
- GAMMAGARD LIQUID is provided as a 10% solution, which is the recommended concentration. If dilution is desired, 5% dextrose in water (D5W) should be used as a diluent. Normal saline should not be used as a diluent.
- The infusion line may be flushed with 0.9% Sodium Chloride. An in-line filter is optional.
- Record the name and lot number of the product in the recipient's records.

2.2 Dose

The recommended dose of GAMMAGARD LIQUID for patients with PI is 300 to 600 mg/kg body weight infused at 3 to 4 week intervals.^{1,2} Adjust dose according to the clinical response.^{3,4} The frequency and dose of immunoglobulin may vary from patient to patient. No randomized controlled clinical trials are available to determine an optimum target trough serum IgG level.

2.3 Administration

The recommended initial infusion rate of GAMMAGARD LIQUID is 0.5 mL/kg/hr (0.8 mg/kg/min). The rate may be increased every 30 minutes, as tolerated, to a maximum rate of 5.0 mL/kg/hr (8 mg/kg/min).

Table 1 provides the recommended infusion rates for GAMMAGARD LIQUID.

Table 1.
Recommended Infusion Rates for GAMMAGARD LIQUID

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
PI	300-600 mg/kg every 3-4 weeks	0.5 mL/kg/hr (0.8 mg/kg/min)	Increase to 5.0 mL/kg/hr (8 mg/kg/min)

Adverse reactions may occur more frequently in patients receiving immune globulin for the first time, upon switching brands to another brand, or if there has been a long interval since the previous infusion.² In such cases, start at lower infusion rates and gradually increase as tolerated.

Monitor patient vital signs throughout the infusion. Certain adverse reactions such as headaches, flushing and changes in pulse rate and blood pressure may be related to the rate of infusion. Slow or stop infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that does not result in recurrence of the symptoms.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer GAMMAGARD LIQUID at the minimum infusion rate practicable. The maximal rate should be less than 3.3 mg/IgG/kg/min (< 2 mL/kg/hr), and consider discontinuation of administration if renal function deteriorates (see WARNINGS AND PRECAUTIONS [5.2, 5.4]).

3. DOSAGE FORMS AND STRENGTHS

GAMMAGARD LIQUID is a liquid solution containing 10% IgG (100 mg/mL).

4. CONTRAINDICATIONS

- GAMMAGARD LIQUID is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immunoglobulin.
- GAMMAGARD LIQUID is contraindicated in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. Anaphylaxis has been reported with the use of GAMMAGARD LIQUID (5.1).

5. WARNINGS AND PRECAUTIONS**5.1. Hypersensitivity**

Severe hypersensitivity reactions may occur, even in patients who had tolerated previous treatment with human normal immunoglobulin. In case of hypersensitivity, discontinue GAMMAGARD LIQUID infusion immediately and institute appropriate treatment.

GAMMAGARD LIQUID contains trace amount of IgA (average concentration of 37µg/mL). Patients with antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. GAMMAGARD LIQUID is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction (see CONTRAINDICATIONS [4]).

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death may occur upon use of IGIV therapy, especially those containing sucrose.⁵ Acute renal dysfunction/failure has been reported in association with infusions of GAMMAGARD LIQUID. Assure that patients are not volume depleted prior to the initiation of infusion of GAMMAGARD LIQUID. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs, etc.), administer GAMMAGARD LIQUID at the minimum rate of infusion practicable (see DOSAGE AND ADMINISTRATION [2]).

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of GAMMAGARD LIQUID and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of GAMMAGARD LIQUID (see DOSAGE AND ADMINISTRATION [2]).

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving GAMMAGARD LIQUID. It is clinically critical to distinguish true hyponatremia from a pseudohyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap; because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a possible predisposition to thromboembolic events.⁶

5.4 Thromboembolic Events

Thromboembolic events, including myocardial infarction, cerebral vascular accident, deep vein thrombosis, and pulmonary embolism have been reported in association with IGIV (including GAMMAGARD LIQUID) (see ADVERSE REACTIONS [6]). Patients at risk for thromboembolic events include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, obesity, diabetes mellitus, acquired or inherited thrombophilic disorder, a history of vascular disease, or a history of a previous thrombotic or thromboembolic event.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see WARNING AND PRECAUTIONS [5.9]). For patients judged to be at risk of developing thrombotic events, administer GAMMAGARD LIQUID at the minimum rate of infusion practicable, not exceeding 3.3 mg IgG/kg/min (< 2 mL/kg/hr) (see DOSAGE AND ADMINISTRATION [2]).

5.5 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur with GAMMAGARD LIQUID administration. 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.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting (*see PATIENT COUNSELING INFORMATION [1.7]*). Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such symptoms and signs, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently with high dose (2 g/kg) IGIV treatment.

5.6 Hemolysis

GAMMAGARD LIQUID contains blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction and, hemolysis.^{5,7} Acute intravascular hemolysis has been reported, and delayed hemolytic anemia can develop due to enhanced RBC sequestration (*see ADVERSE REACTIONS [6]*).

Monitor patients for clinical signs and symptoms of hemolysis (*see WARNINGS AND PRECAUTIONS [5.9]*). If signs and/or symptoms of hemolysis are present after GAMMAGARD LIQUID infusion, perform appropriate confirmatory laboratory testing (*see PATIENT COUNSELING INFORMATION [1.7]*).

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema (TRALI) has been reported to occur following GAMMAGARD LIQUID administration. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment.

Monitor patients for pulmonary adverse reactions (*see PATIENT COUNSELING INFORMATION [1.7]*). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Transmissible Infectious Agents

Because GAMMAGARD LIQUID is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been identified with GAMMAGARD LIQUID.

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 (*see PATIENT COUNSELING INFORMATION [1.7]*).

5.9 Monitoring: Laboratory Tests

- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of GAMMAGARD LIQUID and at appropriate intervals thereafter.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.⁵
- If signs and/or symptoms of hemolysis are present after an infusion of GAMMAGARD LIQUID, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

5.10 Interference with Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield false positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

Serious adverse reactions observed with GAMMAGARD LIQUID were two episodes of aseptic meningitis in one subject.

The most common adverse reactions (reported in > 5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion were headache, fever, fatigue, vomiting, chills, infusion site events, nausea, dizziness, pain in extremity, diarrhea, cough, pruritus and pharyngeal pain (Table 2).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse events were examined among a total of 61 subjects with Primary Immunodeficiency enrolled in a 12 month, multicenter clinical study of GAMMAGARD LIQUID.⁸ For this study, temporally associated adverse events are those occurring during or within 72 hours of completion of an infusion, regardless of causality. Adverse drug reactions (ADRs) are those adverse events that were deemed by the investigators as causally related to the infusion of GAMMAGARD LIQUID.

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

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

Of the 345 temporally related adverse events, those occurring in > 5% of subjects are shown in Table 2. Only one event, headache, occurred in association with more than 5% of infusions.

Table 2.
Adverse Events*, Regardless of Causality, that Occurred within 72 Hours of Infusion

Event	By Infusion (%)	By Subject (%)
Headache	57 (7%)	22 (36%)
Fever	19 (2%)	13 (21%)
Fatigue	18 (2%)	10 (16%)
Vomiting	10 (1%)	9 (15%)
Chills	14 (2%)	8 (23%)
Infusion site events	8 (1%)	8 (13%)
Nausea	9 (1%)	6 (10%)
Dizziness	7 (1%)	6 (10%)
Pain in Extremity	7 (1%)	5 (8%)
Diarrhea	7 (1%)	5 (8%)
Cough	5 (1%)	5 (8%)
Pruritus	5 (1%)	4 (7%)
Pharyngeal Pain	5 (1%)	4 (7%)

* Excluding Infections

Provided in Table 3 are the related adverse events occurring in 5% or more of the 61 subjects from the pivotal multicenter clinical study.

Table 3.
Related Adverse Events Occurring in 5% or More of Subjects

Event	By Infusion (%)	By Subject (%)
Headache	90 (5%)	27 (44%)
Pyrexia	23 (1%)	13 (21%)
Fatigue	26 (1%)	10 (16%)
Rigors	14 (1%)	8 (13%)
Nausea	11 (1%)	8 (13%)
Chills	13 (1%)	7 (12%)
Dizziness	8 (0.4%)	5 (8%)
Vomiting	6 (0.3%)	5 (8%)
Migraine	16 (1%)	4 (7%)
Pain in Extremity	10 (1%)	4 (7%)
Urticaria	8 (0.4%)	4 (7%)
Cough	4 (0.2%)	3 (5%)
Pruritus	4 (0.2%)	3 (5%)
Rash	4 (0.2%)	3 (5%)
Tachycardia	3 (0.2%)	3 (5%)

31 of the 258 of the non-serious adverse reactions were considered unexpected. A total of 14 hospitalizations occurred during the study but none were related to infection.

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

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse reactions have been identified during post-approval use of GAMMAGARD LIQUID:⁶

Hematologic	Hemolysis, Leukopenia, Positive direct Coombs
Infusion Reactions	Hypersensitivity, Anaphylactic shock, Anaphylactic reaction
Neurological	Transient ischemic attack, Tremor, Burning sensation, Cerebral vascular accident
Cardiovascular	Deep vein thrombosis, Hypotension, Phlebitis, Hypertension, Myocardial infarction, Chest pain
Respiratory	Pulmonary embolism, Pulmonary edema, Dyspnea, Oxygen saturation decreased
Gastrointestinal	Abdominal pain
Integumentary	Hyperhidrosis, Allergic dermatitis
Psychiatric	Anxiety, Insomnia
General/Body as a Whole	Pyrexia, Edema

In addition to the events listed above which were observed for GAMMAGARD LIQUID, the following events have been identified for IGIV products in general:

Renal	Acute renal dysfunction/failure, Osmotic nephropathy
Respiratory	Cyanosis, Hypoxemia, Bronchospasm, Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion Related Acute Lung Injury (TRALI),
Integumentary	Bullous dermatitis, Epidermolysis, Erythema multiforme, Stevens-Johnson Syndrome
Cardiovascular	Cardiac arrest, Vascular collapse
Neurological	Coma, Seizures, Loss of consciousness, Aseptic Meningitis Syndrome
Hematologic	Pancytopenia
Gastrointestinal	Hepatic dysfunction

7. DRUG INTERACTIONS

Passive transfer of antibodies may transiently impair the immune responses to live attenuated virus vaccines, such as measles, mumps, rubella and varicella. Inform the immunizing physician of recent therapy with GAMMAGARD LIQUID so that appropriate precautions can be taken (see PATIENT COUNSELING INFORMATION [17]).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with GAMMAGARD LIQUID. It is also not known whether GAMMAGARD LIQUID can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. GAMMAGARD LIQUID should be given to a pregnant woman only if clearly indicated.

8.3 Nursing Mothers

Use of GAMMAGARD LIQUID has not been evaluated in nursing mothers. GAMMAGARD LIQUID should be given to nursing women only if clearly indicated.

8.4 Pediatric Use

GAMMAGARD LIQUID was evaluated in 15 pediatric subjects with PI (7 between the age ranges of 5–11 and 8 between the age ranges of 12–16) in a pivotal multicenter clinical study. The pharmacokinetics, safety and efficacy data were similar to those in the adults. The safety and efficacy of GAMMAGARD LIQUID has not been evaluated in neonates or infants under the age of 2.

8.5 Geriatric Use

Limited information is available for the geriatric use of GAMMAGARD LIQUID. Intravenous administration of GAMMAGARD LIQUID was evaluated in 4 subjects over the age of 65. No overall differences in safety or efficacy were observed for this group. Caution should be exercised in administering GAMMAGARD LIQUID to patients who are at an increased risk for developing renal failure or thromboembolic events (see BOXED WARNING, WARNINGS AND PRECAUTIONS [5.2, 5.4] and DOSAGE AND ADMINISTRATION [2.2]). Infuse GAMMAGARD LIQUID at a rate less than 3.3 mg/IgG/kg/min (< 2mL/kg/hr) for patients over 65 years of age. Do not exceed the recommended dose, and infuse GAMMAGARD LIQUID at the minimum infusion rate practicable.

10. OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity. Patients at particular risk of complications of fluid overload and hyperviscosity include elderly patients and patients with cardiac or renal impairment.

11. DESCRIPTION

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

GAMMAGARD LIQUID is manufactured from large pools of human plasma. IgG preparations are purified from plasma pools using a modified Cohn Oncley cold ethanol fractionation process, as well as cation and anion exchange chromatography.

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

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

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed under extreme conditions (e.g., at minimum S/D concentrations, incubation time and temperature for the S/D treatment). Virus clearance studies for GAMMAGARD LIQUID performed in accordance with good laboratory practices (Table 4) have demonstrated that:

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

Table 4.
Three Dedicated Independent Virus Inactivation/Removal Steps
Mean Log₁₀ Reduction Factors^a (RFs) For Each Virus and Manufacturing Step

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

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

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

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

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

GAMMAGARD LIQUID supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. GAMMAGARD LIQUID also contains a spectrum of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in GAMMAGARD LIQUID have not been fully elucidated.

12.3 Pharmacokinetics

Following infusion, IGIV products show a biphasic decay curve. The initial (α) phase is characterized by an immediate post-infusion peak in serum IgG and is followed by rapid decay due to equilibration between the plasma and extravascular fluid compartments. The second (β) phase is characterized by a slower and constant rate of decay. The commonly cited "normal" half-life of 18 to 25 days is based on studies in which tiny quantities of radiolabeled IgG are injected into healthy individuals. When radio labeled IgG was injected into patients with hypogammaglobulinemia or agammaglobulinemia, highly variable half-lives ranging from 12 to 40 days were observed. In other radio labeled studies, high serum concentrations of IgG, and hypermetabolism associated with fever and infection, have been seen to coincide with a shortened half-life of IgG.

In contrast, however, pharmacokinetic studies in immunodeficient patients are based on the decline of IgG concentrations following infusions of large quantities of gammaglobulin. In such trials, investigators have reported uniformly prolonged half-lives of 26 to 35 days. Pharmacokinetic parameters for GAMMAGARD LIQUID were determined from total IgG levels following the fourth infusion. A total of 61 subjects were enrolled and treated. Of these, 57 had sufficient pharmacokinetic data to be included in the dataset. Pharmacokinetic parameters are presented in Table 5.

Table 5.
Summary of Pharmacokinetic Parameters in 57 Subjects

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

Abbreviations: AUC= area under the curve; C_{max}=maximum concentration; C_{min}= minimum concentration

Median IgG trough levels were maintained between 960 to 1120 mg/dL. These dosing regimens maintained serum trough IgG levels considerably above 450 mg/dL, which is consistent with levels considered to be effective in the treatment of patients with PI.^{1,2,3,4} The elimination half-life of GAMMAGARD LIQUID of 35 days was similar to the half-lives reported for other IGIV products.

14. CLINICAL STUDIES

Use of GAMMAGARD LIQUID in patients with PI is supported by the pivotal clinical study of subjects who were treated with 300 to 600 mg/kg every 21 to 28 days for 12 months. The 61 subjects in this study were between 6 to 72 years of age, 54% female and 46% male, and 93% Caucasian, 5% African-American, and 2% Asian. Three subjects were excluded from the per-protocol analysis due to non-study product related reasons. The annualized rate of specified acute serious bacterial infections, i.e., the mean number of specified acute serious bacterial infections per subject per year¹⁰ was studied (see Table 6).

Table 6.
Summary of Validated Acute Serious Bacterial Infections for the Per-Protocol Analysis

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

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

^b The rate of validated infections was compared with a rate of 1 per subject per year, in accordance with recommendations by the FDA Blood Products Advisory Committee¹⁰

The annualized rate of other specified validated bacterial infections (see Table 7), and the number of hospitalizations secondary to all validated infectious complications were also studied (see Table 6 and Table 7).

Table 7.
Summary of Validated Other Bacterial Infections

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

^a Other bacterial infections that met specific diagnostic requirements

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

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

15. REFERENCES

- Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson Jr. RP, Patel DD, Secord E, Sorenson RU, Wasserman RL, Cunningham-Rundles C, Use of Intravenous Immunoglobulin in Human Disease: A Review of Evidence by Members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol* 2006; 117:S525-53.
- Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005; 94(suppl 1):S1-63.
- Eijkhout HW, Der Meer JW, Kallenberg CG, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med*. 2001;135:165-174.
- Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: Relationship to immunoglobulin therapy over 22 years. *J Allergy Clin Immunology* 2010; 125(6):1354-1360.
- Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfusion Med Rev*. 2003;17:241-251.
- Katz U, Sheonfeld Y. Review: intravenous immunoglobulin therapy and thromboembolic complications. *Lupus* 2005;14:802-8
- Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, et al. Hemolytic transfusion reactions after administration of intravenous intravenous immune (gamma) globulin: a case series analysis. *Transfusion*. 2008; 48:1598-601
- Church JA, Leibl H, Stein MR, et al. Efficacy, safety and tolerability of a new 10% liquid intravenous immune globulin (IGIV 10%) in patients with primary immunodeficiency. *J Clin Immunol* 2006; 26(4):388-395.
- Kreil TR, Berting A, Kistner O, Kindermann J. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. *Transfusion* 2003;43:1023-1028.
- Golding B. IGIV Clinical Endpoints. Presented at: Blood Products Advisory Committee, 65th Meeting. 17 March 2000. Silver Spring, MD.

16. HOW SUPPLIED/STORAGE AND HANDLING

GAMMAGARD LIQUID is supplied in single use bottles containing the labeled amount of functionally active IgG. The packaging of this product is latex-free.

The following presentations of GAMMAGARD LIQUID are available:

NDC Number	Volume	Grams Protein
0944-2700-02	10 mL	1.0
0944-2700-03	25 mL	2.5
0944-2700-04	50 mL	5.0
0944-2700-05	100 mL	10.0
0944-2700-06	200 mL	20.0
0944-2700-07	300 mL	30.0

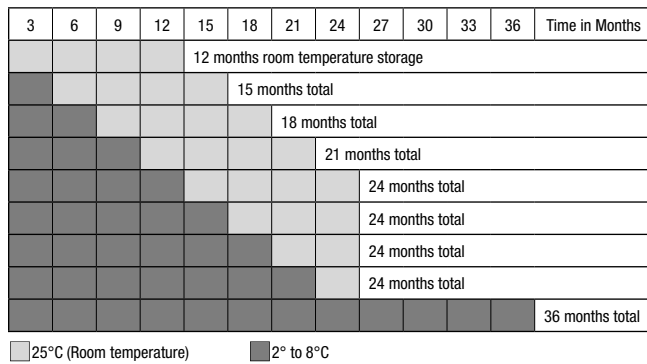
Do not freeze.

Refrigeration: 36 months storage at refrigerated temperature 2° to 8°C (36°-46°F).

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

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

Figure 1: Storage Guidelines
Months from Date of Manufacture



Product cannot be stored at room temperature after 24 months from date of manufacture.

- Example 1: If the product is taken out of the refrigerator after 3 months from date of manufacture, it can be stored for 12 months at room temperature. Total storage time is 15 months.
- Example 2: If the product is taken out of the refrigerator after 21 months from the date of manufacture, it can be stored for 3 months at room temperature. Total storage time is 24 months.

17. PATIENT COUNSELING INFORMATION

Inform patients to immediately report the following signs and symptoms to their healthcare provider:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (see WARNINGS AND PRECAUTIONS [5.2]).
- Acute chest pain, shortness of breath, leg pain, and swelling of the legs/feet, numbness in the face or extremities, weakness or paralysis, severe headache, confusion, visual disturbances (see WARNINGS AND PRECAUTIONS [5.4]).
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (see WARNINGS AND PRECAUTIONS [5.5]).
- Trouble breathing, chest pain, blue lips or extremities, or fever that can occur 1 to 6 hours after an infusion of GAMMAGARD LIQUID (see WARNINGS AND PRECAUTIONS [5.5]).
- Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine (see WARNINGS AND PRECAUTIONS [5.6]).

Inform patients that GAMMAGARD LIQUID is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the vCJD agent). The risk of GAMMAGARD LIQUID transmitting an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing. Patients should report any symptoms that concern them which might be caused by virus infections (see WARNINGS AND PRECAUTIONS [5.8]).

Inform patients that GAMMAGARD LIQUID can interfere with their immune response to live viral vaccines such as measles, mumps rubella and varicella, and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see DRUG INTERACTIONS [7]).

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

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Issued: December 2010

