GAMMAGARD LIQUID
Immune Globulin Infusion (Human) 10%

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 Infusion (Human), 10% Solution, for intravenous and subcutaneous administration

Initial U.S. Approval: 2005

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning

- **Thrombosis may occur with immune globulin products, including GAMMAGARD LIQUID. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products including GAMMAGARD LIQUID. Renal dysfunction and acute failure occur more commonly with IGIV products containing sucrose. GAMMAGARD LIQUID does not contain sucrose.**
- **For patients at risk of thrombosis, administer GAMMAGARD LIQUID at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity.**

RECENT MAJOR CHANGES

- Boxed Warning; Warnings and Precautions, Thrombosis (5.4) 09/2013

INDICATIONS AND USAGE

- GAMMAGARD LIQUID is an immune globulin infusion (human) indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older. (1)
- GAMMAGARD LIQUID is indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy [MMN].(1).

DOSAGE AND ADMINISTRATION

Dose	Initial Infusion Rate	Maintenance Infusion Rate
Intravenous Administration		
	PI	
300 to 600 mg/kg every 3 to 4 weeks based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes	Increase every 30 minutes (if tolerated) up to 5 mL/kg/hr (8 mg/kg/min)
	MMN	
Dose range 0.5 to 2.4 grams/kg/month based on clinical response	0.5 mL/kg/hr (0.8 mg/kg/min)	Infusion rate may be advanced if tolerated to 5.4 mL/kg/hr (9 mg/kg/min)
Subcutaneous Administration:		
	PI	
Initial Dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level (2.2).	40 kg BW and greater: 30 mL/site at 20 mL/hr/site Under 40 kg BW: 20 mL/site at 15 mL/hr/site	40 kg BW and greater: 30 mL/site at 20 to 30 mL/hr/site Under 40 kg BW: 20 mL/site at 15 to 20 mL/hr/site

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue GAMMAGARD LIQUID if renal function deteriorates. (2.3, 5.2)
- For patients at risk of renal dysfunction or thrombotic events, administer GAMMAGARD LIQUID at the minimum infusion rate practicable. (2.3, 5.2, 5.4)

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DOSAGE FORMS AND STRENGTHS

- Aqueous solution containing 10% IgG (100 milligram/mL) (3)

CONTRAINDICATIONS

- Anaphylactic or severe systemic hypersensitivity 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 acute renal failure. (5.2)
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur. (5.3)
- Thrombosis may occur. Monitor for signs and symptoms of thrombosis and assess blood viscosity for those at risk for hyperviscosity. (5.4)
- Aseptic Meningitis Syndrome (AMS) may occur. (5.5)
- Hemolytic anemia can develop. Monitor 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)
- Product is made from human blood and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease agent (5.8)

ADVERSE REACTIONS

Serious adverse reactions which occurred in the clinical trials were aseptic meningitis, pulmonary embolism, and blurred vision. (6.1)

The most common adverse reactions observed in ≥5% of patients were (6.1):

PI: Intravenous Administration: Headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.

Subcutaneous Administration: Infusion site (local) event, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.

MMN: Headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

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, rubella, and varicella. (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 17 for PATIENT COUNSELING INFORMATION and FDA APPROVED PATIENT LABELING.

Revised: 04/2014

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including GAMMAGARD LIQUID. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. [see *Warnings and Precautions (5.4), Patient Counseling Information (17)*]**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients with immune globulin intravenous (IGIV) products. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMMAGARD LIQUID does not contain sucrose.**
- **For patients at risk of thrombosis, administer GAMMAGARD LIQUID at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk of hyperviscosity. [see *Dosage and Administration (2.3) and Warnings and Precautions (5.4)*]**

1 INDICATIONS AND USAGE

GAMMAGARD LIQUID is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older. 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]

GAMMAGARD LIQUID is indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Table 1.
Dosage and Administration

Dose	Initial Infusion rate	Maintenance Infusion rate
Intravenous Administration		
Primary Immunodeficiency		
300 to 600 milligram/kg every 3 to 4 weeks based on clinical response	0.5 mL/kg/hr (0.8 milligram/kg/min) for 30 minutes	Increase every 30 minutes (if tolerated) up to 5 mL/kg/hr (8 milligram/kg/min)
Multifocal Motor Neuropathy		
Dose range 0.5 to 2.4 grams/kg/month based on clinical response (14)	0.5 mL/kg/hr (0.8 milligram/kg/min)	Infusion rate may be increased if tolerated up to 5.4 mL/kg/hr (9 milligram/kg/min)
Subcutaneous Administration:		
Primary Immunodeficiency		
Initial Dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level (2.2).	40 kg BW and greater: 30 mL/site at 20 mL/hr/site. Under 40 kg BW: 20 mL/site at 15 mL/hr/site.	40 kg BW and greater: 30 mL/site at 20 to 30 mL/hr/site. Under 40 kg BW: 20 mL/site at 15 to 20 mL/hr/site.

DOSE ADJUSTMENTS FOR INTRAVENOUS ADMINISTRATION IN PATIENTS WITH PI

Adjust dose according to IgG levels and clinical response, as the frequency and dose of immune globulin may vary from patient to patient.
No randomized controlled clinical trials are available to determine an optimum trough serum IgG level for intravenous treatment. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Prior to switching from intravenous to subcutaneous treatment, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. Start the initial subcutaneous dose approximately one week after the last intravenous infusion.

DOSE ADJUSTMENTS FOR INTRAVENOUS ADMINISTRATION IN MMN

The dose may need to be adjusted to achieve the desired clinical response. In the clinical study, the dose ranged between 0.5 to 2.4 grams/kg/month (see Table 1). While receiving GAMMAGARD LIQUID, 9% of subjects in the clinical study experienced neurological decompensation that required an increase in dose. In order to avoid worsening of muscle weakness in patients, dose adjustment may be necessary.

DOSE ADJUSTMENTS FOR SUBCUTANEOUS ADMINISTRATION FOR PI ONLY

Based on the results of clinical studies, the expected increase in serum IgG trough level while on weekly subcutaneous treatment, at the dose adjusted to provide a comparable AUC, is projected to be approximately 281 milligram/dL higher than the last trough level during prior stable intravenous treatment. To calculate the target trough IgG level for subcutaneous treatment, add 281 milligram/dL to the IgG trough level obtained after the last intravenous treatment.

To guide dose adjustment, calculate the difference between the patient's target serum IgG trough level and the IgG trough level during subcutaneous treatment. Find this difference in the columns of Table 2 and the corresponding amount (in mL) by which to increase (or decrease) the weekly dose based on the patient's body weight. If the difference between measured and target trough levels is less than 100 milligram/dL then no adjustment is necessary. **However, the patient's clinical response should be the primary consideration in dose adjustment.**

Table 2.
Change in Weekly Dose of GAMMAGARD LIQUID for Intended IgG Trough Level Adjustment[a]

	Difference between Measured and Target IgG Trough Levels			
Body Weight	**100 mg/dL**	**200 mg/dL**	**300 mg/dL**	**400 mg/dL**
10 kg	2 mL	4 mL	6 mL	8 mL
20 kg	4 mL	8 mL	11 mL	15 mL
30 kg	6 mL	11 mL	17 mL	23 mL
40 kg	8 mL	15 mL	23 mL	30 mL
50 kg	9 mL	19 mL	28 mL	38 mL
60 kg	11 mL	23 mL	34 mL	45 mL
70 kg	13 mL	26 mL	40 mL	53 mL
80 kg	15 mL	30 mL	45 mL	60 mL
90 kg	17 mL	34 mL	51 mL	68 mL
100 kg	19 mL	38 mL	57 mL	75 mL
110 kg	21 mL	42 mL	62 mL	83 mL
120 kg	23 mL	45 mL	68 mL	91 mL
130 kg	25 mL	49 mL	74 mL	98 mL
140 kg	26 mL	53 mL	79 mL	106 mL

[a] Derived using a linear approximation to the nomogram method with a slope of 5.3 kg/dL.

Example 1: A patient with a body weight of 80 kg has a measured IgG trough level of 800 milligram/dL and the target trough level is 1000 milligram/dL. The desired target trough level difference is 200 milligram/dL (1000 milligram/dL minus 800 milligram/dL). The weekly dose of GAMMAGARD LIQUID should be **increased** by 30 mL (3.0 gm).

Example 2: A patient with a body weight of 60 kg has a measured IgG trough of 1000 milligram/dL and the target trough level is 800 milligram/dL. The desired target trough level difference is 200 milligram/dL (800 milligram/dL minus 1000 milligram/dL). The weekly dose of GAMMAGARD LIQUID should be **decreased** by 23 mL (2.3 gm).

2.2 Preparation and Handling

- Inspect the drug product visually for particulate matter and discoloration prior to administration. GAMMAGARD LIQUID is a clear or slightly opalescent, colorless or pale yellow solution. Do not use if the solution is cloudy, turbid, or if it contains particulates.
- GAMMAGARD LIQUID vial is for single use only. Any vial that has been entered should be used promptly. Partially used vials should be discarded. GAMMAGARD LIQUID contains no preservative.

- Allow refrigerated product to come to room temperature before use. DO NOT MICROWAVE.
- Do not shake.
- Do not mix with other products.
- Do not use normal saline as a diluent. If dilution is desired, 5% dextrose in water (D5W) should be used as a diluent.
- The infusion line may be flushed with normal saline. An in-line filter is optional.
- Record the name and lot number of the product in the recipient's records.

2.3 Administration

INTRAVENOUS

Table 3.
Infusion Rates for Intravenous Administration

	PI	MMN
Initial	0.5 mL/kg/hr (0.8 milligram/kg/min) for 30 minutes	Increasing rates of infusion starting at 0.5mL/kg/h (0.8 milligram/kg/min)
Subsequent	Increase every 30 minutes (if tolerated) up to 5 mL/kg/hr (8 milligram/kg/min)	Increasing to a maximum rate of 5.4 mL/kg/hr if tolerated (9 milligram/kg/min)

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.

Adverse reactions may occur more frequently in patients receiving immune globulin for the first time, upon switching brands 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.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients over 65 years of age or judged to be at risk for renal dysfunction or thrombotic events, administer GAMMAGARD LIQUID at the minimum infusion rate practicable. In such cases, the maximal rate should be less than 3.3 milligram/kg/min (<2mL/kg/hr), and consider discontinuation of administration if renal function deteriorates [see *Warnings and Precautions (5.2, 5.4)* and *Use In Specific Populations (8.5)*].

SUBCUTANEOUS FOR PI

Table 4.
Infusion Rates for Subcutaneous Administration

	40 kg BW and greater	Under 40 kg BW
Initial	30 mL/site at a rate of 20 mL/hr/site.	20 mL/site at a rate of 15 mL/hr/site
Maintenance	30 mL/site at a rate of 20 to 30 mL/hr/site	20 mL/site at a rate of 15 to 20 mL/hr/site

Selection of Infusion Site: Suggested areas for subcutaneous infusion of GAMMAGARD LIQUID are abdomen, thighs, upper arms, or lower back. Infusion sites should be at least two inches apart, avoiding bony prominences. Rotate sites each week.

Volume per Site: The weekly dose (mL) should be divided by 30 or 20, based on patient weight above, to determine the number of sites required. Simultaneous subcutaneous infusion at multiple sites can be facilitated by use of a multi-needle administration set.

Rate of Infusion for Patients 40 kg and greater (88 lbs): If multiple sites are used, the rate set on the pump should be the rate per site multiplied by the number of sites (e.g., 30 mL x 4 sites = 120 mL/hr). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 240 mL/hr.

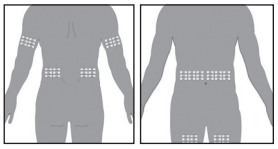
Rate of Infusion for Patients under 40 kg (88 lbs): If multiple sites are used, the rate set on the pump should be the rate per site multiplied by the number of sites (e.g., 20 mL x 3 sites = 60 mL/hr). The number of simultaneous sites should be limited to 8, or maximum infusion rate of 160 mL/hr.

Instructions for Subcutaneous Administration: Instruct patients to observe the following procedures:

1. **Aseptic technique—**Use aseptic technique when preparing and infusing GAMMAGARD LIQUID.
2. **Assemble supplies—**Set up a clean work area and gather all supplies necessary for the subcutaneous infusion: vial(s) of GAMMAGARD LIQUID, ancillary supplies, sharps container and pump. If GAMMAGARD LIQUID has already been pooled into a bag or a syringe, skip to Step 5.
3. **Product preparation—**Remove the protective cap from the vial to expose the center of the vial. Wipe the stopper with an alcohol pad and allow to dry.

4. **Withdraw GAMMAGARD LIQUID from the vials—**Attach a sterile syringe to a needle and draw air into the syringe barrel equal to the amount of product to be withdrawn. Inject the air into the vial and withdraw the desired volume of GAMMAGARD LIQUID. If multiple vials are required to achieve the desired dose, repeat this step.

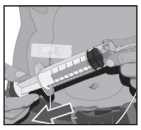
5. **Prepare the infusion pump and tubing—**Follow the manufacturer's instructions for preparing the pump and administration tubing, if needed. Be sure to prime the pump tubing to ensure that no air is left in the tubing and needle.
6. **Select the infusion sites—**Select the number of infusion sites depending on the volume of the total dose. See *Administration (2.3)* for recommended maximum volumes and rates. Potential sites for infusion include the back of arms, abdomen, thighs, and lower back (see Figure below). Ensure sites are at least 2 inches apart; avoid bony prominences.



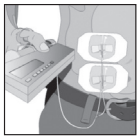
7. **Cleanse the infusion site(s)—**Cleanse the infusion site(s) with an antiseptic skin preparation (e.g., alcohol pad) using a circular motion working from the center of the site and moving to the outside. Allow to dry.

8. **Insert the needle—**Choose the correct needle length to assure that GAMMAGARD LIQUID is delivered into the subcutaneous space. Grasp the skin and pinch at least one inch of skin between two fingers. Insert needle at a 90-degree angle with a darting motion into the subcutaneous tissue. Secure the needle.

9. **Check for proper needle placement—**Prior to the start of infusion, check each needle for correct placement to make sure that a blood vessel has not been punctured. Gently pull back on the attached syringe plunger and monitor for any blood return in the needle set. If you see any blood, remove and discard the needle set. Repeat priming and needle insertion steps in a different infusion site with a new needle set.



10. **Secure the needle to the skin—**Secure the needle(s) in place by applying a sterile protective dressing over the site.



11. **Start infusion of GAMMAGARD LIQUID—**Follow the manufacturer's instructions to turn pump on.
12. **Document the infusion—**Remove the peel-off label with product lot number and expiration date from the GAMMAGARD LIQUID vial and place in treatment diary/log book to keep track of the product lots used. Keep the treatment diary/log book current by recording the time, date, dose, product label and any reactions after each infusion.
13. **Remove needle set—**After the infusion is complete, remove the needle set and gently press a small piece of gauze over the needle insertion site and cover with a protective dressing. Discard any unused solution and disposable supplies in accordance with local requirements.

3 DOSAGE FORMS AND STRENGTHS

GAMMAGARD LIQUID is an aqueous solution containing 10% IgG (100 milligram/mL).

4 CONTRAINDICATIONS

4.1. Hypersensitivity Reaction to Immune Globulins

GAMMAGARD LIQUID is contraindicated in patients who have a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.

4.2. IgA Sensitive Patients with History of Hypersensitivity Reactions

GAMMAGARD LIQUID is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. Anaphylaxis has been reported with the intravenous use of GAMMAGARD LIQUID and is theoretically possible following subcutaneous administration [see *Hypersensitivity (*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 immune globulin. 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 treatment, especially those containing sucrose[3]. 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 intravenously at the minimum rate of infusion practicable (not exceeding 3.3 milligram IgG/kg/min (<2 mL/kg/hr) [see *Dosage and Administration (2.3)*].

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 (2.3)*].

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving GAMMAGARD LIQUID. It is 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 predisposition to thromboembolic events[4].

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including GAMMAGARD LIQUID. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

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. For patients at risk of thrombosis, administer GAMMAGARD LIQUID at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity [see *Boxed Warning, Dosage and Administration (2.3), Patient Counseling Information (17)*].

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur with IGIV treatment, and has been reported with intravenous use of GAMMAGARD LIQUID. 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 (*17*)*]. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred milligram/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 grams/kg) IGIV treatment and/or rapid infusion of IGIV.

5.6 Hemolysis

GAMMAGARD LIQUID, 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)][5,6]. Delayed hemolytic anemia can develop subsequent to GAMMAGARD LIQUID therapy due to enhanced RBC sequestration; acute hemolysis, consistent with intravascular hemolysis, has been reported [see *Adverse Reactions (*6*)*][5-8].

The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥2 grams/kg, single administration or divided over several days) and non-O blood group.[5] Underlying inflammatory state in an individual patient may increase the risk of hemolysis[5] but its role is uncertain.[8,9]

Monitor patients for clinical signs and symptoms of hemolysis [see *Warnings and Precautions (*5.9*)*], particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema (TRALI) has been reported in patients following treatment with IGIV products, including GAMMAGARD LIQUID. 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 (*17*)]*. 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 Transmittable Infectious Agents

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

All infections thought by a physician to possibly 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.).

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[3,4].
- 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

PI: Intravenous: The serious adverse reaction seen during intravenous treatment in the clinical trials for PI was aseptic meningitis. The most common adverse reactions for PI (observed in ≥5% of subjects) were headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur.

Subcutaneous: No serious adverse reactions were observed during the clinical trial for subcutaneous treatment. The most common adverse reactions during subcutaneous treatment (observed in ≥5% of PI subjects) were infusion site (local) event, headache, fatigue, heart rate increased, pyrexia, abdominal pain upper, nausea, vomiting, asthma, blood pressure systolic increased, diarrhea, ear pain, aphthous stomatitis, migraine, oropharyngeal pain, and pain in extremity.

MMN: The serious adverse reactions in the clinical trial for MMN were pulmonary embolism and blurred vision. The most common adverse reactions for MMN (observed in ≥5% of subjects) were headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

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.

PI: INTRAVENOUS ADMINISTRATION

The safety of GAMMAGARD LIQUID intravenous infusion was evaluated in 61 subjects[10].

Fifteen adverse reactions in 8 subjects were serious. Of these, two episodes of aseptic meningitis in one patient were deemed possibly related to the infusion of GAMMAGARD LIQUID.

There were 400 non-serious adverse reactions. Of these, 217 were rated as mild (transient discomfort that resolves spontaneously or with minimal intervention), 164 were rated as moderate (limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae), and 19 were rated as severe (marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae). All of the severe non-serious adverse experiences were transient, did not lead to hospitalization, and resolved without complication. One subject withdrew from the study due to a non-serious adverse experience (papular rash).

Adverse reactions with a frequency of ≥5% (defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period) are shown in Table 5.

Table 5.

Adverse Reactions Occurring in ≥5% of Subjects

Events	By Infusion N (%) (N=1812 Infusions)	By Subject N (%) (N=61 Subjects)
Headache	94 (5.2%)	29 (47.5%)
Fatigue	33 (1.8%)	14 (23.0%)
Pyrexia	28 (1.5%)	17 (27.9%)
Nausea	17 (0.9%)	11 (18.0%)
Chills	14 (0.8%)	8 (13.1%)
Rigors	14 (0.8%)	8 (13.1%)
Pain in extremity	13 (0.7%)	7 (11.5%)
Diarrhea	12 (0.7%)	9 (14.8%)
Migraine	12 (0.7%)	4 (6.6%)
Dizziness	11 (0.6%)	8 (13.1%)
Vomiting	11 (0.6%)	9 (14.8%)
Cough	9 (0.5%)	8 (13.1%)
Urticaria	9 (0.5%)	5 (8.2%)
Asthma	7 (0.4%)	6 (9.8%)
Pharyngolaryngeal pain	7 (0.4%)	5 (8.2%)
Rash	6 (0.3%)	4 (6.6%)
Arthralgia	5 (0.3%)	4 (6.6%)
Myalgia	5 (0.3%)	5 (8.2%)
Oedema peripheral	5 (0.3%)	5 (8.2%)
Pruritus	5 (0.3%)	4 (6.6%)
Cardiac murmur	4 (0.2%)	4 (6.6%)

PI: SUBCUTANEOUS ADMINISTRATION

The safety of GAMMAGARD LIQUID in subcutaneous infusion was evaluated in 47 subjects[11].

Adverse reactions with a frequency of ≥5% (defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period) are shown in Table 6.

Table 6.

Adverse Reactions Occurring in ≥5% of Subjects

Events	By Infusion N (%) (N=2294 infusions)	By Subject N (%) (N=47 Subjects)
Infusion site (local) event	55 (2.4%)	21 (44.7%)
Headache	31 (1.4%)	19 (40.4%)
Fatigue	11 (0.5%)	7 (14.9%)
Heart rate increased	11 (0.5%)	3 (6.4%)
Pyrexia	11 (0.5%)	9 (19.1%)
Abdominal pain upper	9 (0.4%)	5 (10.6%)
Nausea	7 (0.3%)	3 (6.4%)
Vomiting	7 (0.3%)	5 (10.6%)
Asthma	6 (0.3%)	4 (8.5%)
Blood pressure systolic increased	6 (0.3%)	3 (6.4%)
Diarrhea	5 (0.2%)	3 (6.4%)
Ear pain	4 (0.2%)	3 (6.4%)
Aphthous stomatitis	3 (0.1%)	3 (6.4%)
Migraine	3 (0.1%)	3 (6.4%)
Oropharyngeal pain	3 (0.1%)	3 (6.4%)
Pain in extremity	3 (0.1%)	3 (6.4%)

Of the 348 non-serious ARs, 228 were rated as mild (transient discomfort that resolves spontaneously or with minimal intervention), 112 were rated as moderate (limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae), and 8 were rated as severe (marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae). Neither of the severe ARs required hospitalization or resulted in sequelae.

Local AEs: Local AEs reported as mild (transient discomfort that resolves spontaneously or with minimal intervention) were rash, erythema, edema, hemorrhage, and irritation. Local AEs reported as mild or moderate (limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae) were pain, hematoma, pruritus, and swelling.

One subject withdrew from the study after 10 treatments with GAMMAGARD LIQUID subcutaneous infusion (2.5 months) due to increased fatigue and malaise.

The overall rate of local ARs (excluding infections) during the subcutaneous treatment periods was 2.4% per infusion. In subcutaneous naïve patients, the incidence of local ARs (N=1757 infusions) was 2.8% (2.2% mild and 0.6% moderate with no severe AEs). In the subjects who were subcutaneous experienced (N=537 infusions), the incidence of local AEs was 1.1% (1.1% mild, and no moderate or severe AEs).

In the clinical study after all subcutaneous doses were adjusted, all subjects but one reached their maximum rate allowed in the protocol, 20 mL/site/hour if weight was below 40 kg and 30/mL/hour for weight 40 kg and greater, for one or more of the infusions. 70% (31 of 44) of these subjects opted for the highest rate for all infusions. No subject restricted the rate due to an AR. In the clinical study, median duration of each weekly infusion was 1.2 hours (range: 0.8-2.3 hours) after all subcutaneous doses were adjusted. The rate set on the pump was that rate per site multiplied by the number of sites, with no maximum.

During all subcutaneous treatment periods, 99.8% of infusions were completed without a reduction, interruption, or discontinuation for tolerability reasons. The proportion of subjects who experienced local ARs (excluding infections) was highest immediately following the switch from intravenous to subcutaneous treatment in all age groups. The rate of all local ARs per infusion immediately after switching from intravenous to subcutaneous treatment was 4.9% (29/595), decreasing to 1.5% (8/538) by the end of the study and to 1.1% (10/893) in the Study Extension. Over subsequent subcutaneous infusions, there was a decrease of local ARs.

Eight (17%) subjects experienced a local adverse reaction during the first infusion, but that decreased to 1 (2.2%) for the subsequent infusions, ranging from 0 to 4 (8.7%) during the first year of subcutaneous treatment. No subject reported a local adverse reaction from week 53 to end of study at week 68.

MMN: INTRAVENOUS INFUSION

The safety of GAMMAGARD LIQUID was evaluated in 44 subjects with MMN who received a total of 983 infusions. Two serious adverse reactions, pulmonary embolism, and blurred vision occurred.

In the study, among the 317 non-serious AEs, 176 were considered ARs. Of these, 126 were mild (transient discomfort that resolves spontaneously or with minimal intervention), 37 were moderate (limited impairment of function and resolves spontaneously or with minimal intervention with no sequelae) and 13 were severe (marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae).

Adverse reactions with a frequency of ≥5% (defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period) are shown in Table 7.

Table 7.
Adverse Reactions Occurring in ≥5% of MMN Subjects

Events	GAMMAGARD LIQUID		Placebo	
	By Infusion N (%) (N=983 Infusions)	By Subject N (%) (N=44 Subjects)	By Infusion N (%) (N=129 Infusions)	By Subject N (%) (N=43 Subjects)
Headache	28 (2.85%)	14 (31.82%)	3 (2.33%)	2 (4.65%)
Chest Discomfort	3 (0.31%)	3 (6.82%)	0 (0.00%)	0 (0.00%)
Muscle Spasms	3 (0.31%)	3 (6.82%)	0 (0.00%)	0 (0.00%)
Muscular weakness	4 (0.41%)	3 (6.82%)	1 (0.78%)	1 (2.33%)
Nausea	28 (2.85%)	3 (6.82%)	2 (1.55%)	1 (2.33%)
Oropharyngeal pain	4 (0.41%)	3 (6.82%)	0 (0.00%)	0 (0.00%)
Pain in extremity	4 (0.41%)	3 (6.82%)	1 (0.78%)	1 (2.33%)

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

INTRAVENOUS ADRs

Hematologic	Leukopenia
Infusion Reactions	Anaphylactic shock, anaphylactic reaction
Neurological	Transient ischemic attack, tremor, burning sensation
Cardiovascular	Hypotension, phlebitis, hypertension, chest pain
Respiratory	Pulmonary edema, dyspnea, oxygen saturation decreased
Gastrointestinal	Abdominal pain
Integumentary	Hyperhidrosis, allergic dermatitis
Psychiatric	Anxiety, insomnia

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	Osmotic nephropathy
Respiratory	Cyanosis, hypoxemia, bronchospasm, apnea, Acute Respiratory Distress Syndrome (ARDS)
Integumentary	Bullous dermatitis, epidermolysis, erythema multiforme, Stevens-Johnson Syndrome
Cardiovascular	Cardiac arrest, vascular collapse
Neurological	Coma, seizures, loss of consciousness
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 mumps, rubella and varicella for up to 6 months and for a year or more to measles (rubeola). 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. Immune globulins 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

It is not known whether GAMMAGARD LIQUID is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GAMMAGARD LIQUID is administered to a nursing woman.

8.4 Pediatric Use

PI

GAMMAGARD LIQUID administered intravenously was evaluated in 15 pediatric subjects with PI (7 were 2 to <12 years old and 8 were 12 to <16) in a multicenter clinical study. GAMMAGARD LIQUID administered subcutaneously was evaluated in 18 pediatric subjects with PI (14 were 2 to <12 years old and 4 were 12 to <16) in another multicenter clinical study. The safety and efficacy profiles were similar to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Safety and efficacy of GAMMAGARD LIQUID in pediatric patients below the age of 2 have not been established.

MMN

Safety and effectiveness in pediatric patients with MMN have not been established.

8.5 Geriatric Use

PI

Limited information is available for the geriatric use of GAMMAGARD LIQUID. GAMMAGARD LIQUID administered intravenously and subcutaneously was evaluated in two PI studies with a total of 8 subjects over the age of 65 years. No differences in safety or efficacy were observed for this group. Monitor patients who are at an increased risk for developing renal failure or thrombotic events. Do not exceed the recommended dose, and infuse at the minimum intravenous infusion rate practicable [see *Boxed Warning, Warnings and Precautions (*5.2, 5.4*) and Dosage and Administration (*2.3*)*].

MMN

GAMMAGARD LIQUID was administered intravenously for treatment of MMN in 5 subjects 65 years and above. There were insufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects [see *Boxed Warning, Warnings and Precautions (*5.2, 5.4*) and Dosage and Administration (*2.3*)*].

10 OVERDOSAGE

With intravenous administration, overdose of GAMMAGARD LIQUID may lead to fluid overload and hyperviscosity. Patients at risk of complications of fluid overload and hyperviscosity include elderly patients and those with cardiac or renal impairment.

11 DESCRIPTION

GAMMAGARD LIQUID 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 milligram/mL protein. At least 98% of the protein is immune globulin, 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 to be negative.

To further improve the margin of safety, validated virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent (S/D) treatment[12], 35 nm nanofiltration, and a low pH incubation at elevated temperature (30°C to 32°C). 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. S/D treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes[12].

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 are summarized in Table 8.

Table 8.
Three Dedicated Independent Virus Inactivation/Removal Steps
Mean Log_{10} Reduction Factors[a] (RFs) For Each Virus and Manufacturing Step

Virus type	Enveloped RNA			Enveloped DNA	Non-enveloped RNA		Non-enveloped DNA
Family	Retroviridae	Flaviviridae		Herpesviridae	Picornaviridae		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. Log_{10} 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

PI: INTRAVENOUS ADMINISTRATION

Following intravenous 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 radiolabeled IgG was injected into patients with hypogammaglobulinemia or agammaglobulinemia, highly variable half-lives ranging from 12 to 40 days were observed. In other radiolabeled studies, high serum concentrations of IgG, and hypermetabolism associated with fever and infection, have been seen to coincide with a shortened half-life of IgG.

In contrast, however, pharmacokinetic studies in immunodeficient patients are based on the decline of IgG concentrations following infusions of large quantities of immune globulin. 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 in 61 subjects with primary humoral immunodeficiency treated intravenously with the product every 3 or 4 weeks according to the regimen used prior to entering the study. Of these, 57 had sufficient pharmacokinetic data to be included in the dataset. The median weight-adjusted dose per subject was 455 milligram/kg/4 weeks with a range of 262 to 710. Pharmacokinetic parameters are presented in Table 9.

Table 9.
Summary of Intravenous Pharmacokinetic Parameters in 57 Subjects

Parameter	Median	95% Confidence Interval
Dose of IgG (milligram/kg/4 weeks)	**455**	**Range: 262-710**
Elimination Half-Life (T ½ days)	35	(31, 42)
$AUC_{0\text{-}21d}$ (milligram·days/dL)	29139	(27494, 30490)
C_{max} (Peak, milligram/dL)	2050	(1980, 2200)
C_{min} (Trough, milligram/dL)	1030	(939, 1110)
Incremental recovery (milligram/dL)/(milligram/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 milligram/dL. These dosing regimens maintained serum trough IgG levels generally considered adequate to prevent bacterial infections. The elimination half-life of GAMMAGARD LIQUID of 35 days was similar to the half-lives reported for other IGIV products.

PI: SUBCUTANEOUS ADMINISTRATION

Pharmacokinetic (PK) parameters of subcutaneously administered GAMMAGARD LIQUID were evaluated in subjects with primary immunodeficiency (PI) who were 12 years and older during a clinical study [see *Clinical Studies (14)]*. Subjects were treated intravenously for 12 weeks with GAMMAGARD LIQUID and then switched to weekly subcutaneous GAMMAGARD LIQUID infusions. Initially, all subjects were treated for a minimum of 12 weeks at a subcutaneous dose that was 130% of the intravenous dose. A comparison of the area under the curve (AUC) for intravenous and subcutaneous infusions done on the first 15 adult subjects determined that the subcutaneous dose required to provide an exposure from subcutaneous administration that was not inferior to the exposure from intravenous administration was 137% of the intravenous dose. Subsequently, all subjects were treated with this dose for 6 weeks after which the dose was individualized for all subjects using the trough IgG levels, as described below. After a minimum of 8 weeks at this subcutaneous dose, the PK evaluation was conducted on 32 subjects 12 years of age or older.

The mean adjusted dose at the end of the study was 137.3% (125.7 to 150.8) of the intravenous dose for subjects 12 years and older, and 141.0% (100.5 to 160.0) for subjects under the age of 12. Thus, there was not a significant dosing difference required for children. At this dose adjustment, the geometric mean ratio of the AUC for subcutaneous vs. intravenous GAMMAGARD LIQUID administration was 95.2% (90% confidence limit 92.3 to 98.2). The peak IgG level occurred 2.9 (1.2 to 3.2) days after subcutaneous administration.

The pharmacokinetic parameters of GAMMAGARD LIQUID administered intravenously compared to subcutaneously in the clinical trial are shown in Table 10. The mean peak IgG levels were lower (1393 ± 289 milligram/dL) during subcutaneous treatment with GAMMAGARD LIQUID compared to when it was administered intravenously (2240 ± 536 milligram/dL), consistent with the lower weekly dose compared to the dose administered every 3 or 4 weeks intravenously. In contrast, the mean trough levels were higher with GAMMAGARD LIQUID given subcutaneously (1202 ± 282 milligram/dL), compared to those when given intravenously (1050 ± 260 milligram/dL), a result of both higher monthly dose and more frequent dosing. The median IgG trough level during intravenous treatment in this clinical trial, 1010 milligram/dL (95% CI: 940 to 1240), was similar to the median value of 1030 milligram/dL (95% CI: 939 to 1110) during the intravenous clinical trial shown above in Table 9. By contrast, the median trough IgG level during subcutaneous treatment for the study was higher, at 1260 milligram/dL (95% CI: 1060 to 1400).

Table 10.
Pharmacokinetic Parameters of Subcutaneously Administered GAMMAGARD LIQUID Compared to GAMMAGARD LIQUID Administered Intravenously

	Subcutaneous Administration	Intravenous Administration
Number of Subjects	**32**	**32**
Dose[1] (milligram/kg)		
Mean ± SD	182.6 ± 48.4	133.2 ± 36.9
Range (min to max)	94.2 to 293.8	62.7 to 195.4
IgG Peak Levels (milligram/dL)		
Mean ± SD	1393 ± 289	2240 ± 536
Range (min to max)	734 to 1900	1130 to 3610
IgG Trough Levels (milligram/dL)		
Mean ± SD	1202 ± 282	1050 ± 260
Range (min to max)	621 to 1700	532 to 1460
AUC[2] (days*milligram/dL)		
Mean ± SD	9176 ± 1928	9958 ± 2274
Range (min to max)	4695 to 12468	5097 to 13831
Clearance [mL/kg/day]		
Mean ± SD	2.023 ± 0.528	1.355 ± 0.316
Range (min to max)	1.225 to 3.747	0.880 to 2.340

1. Weekly equivalent dose
2. Standardized to a 7 day interval

MMN: INTRAVENOUS ADMINISTRATION

No full pharmacokinetic study was conducted in patients with MMN. However, trough levels of IgG were measured in this patient population (n = 44; five 12 week study parts). The median serum trough level of total IgG over all study parts regardless of dosing intervals and length of infusion cycles, was 16.40 g/L (95% confidence interval: 15.7 to 17.1). During placebo administration, the median trough level was 12.35 g/L (95% CI: 10.6 to 13.6). The relationship between serum IgG concentration and efficacy was not assessed.

14 CLINICAL STUDIES

PI: INTRAVENOUS ADMINISTRATION

Intravenous use of GAMMAGARD LIQUID is supported by a study in 61 subjects who were treated with 300 to 600 milligram/kg every 21 to 28 days for 12 months. The age range of the subjects was between 6 to 72 years: 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 year was studied (see Table 11).

Table 11.
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 Committee.

The annualized rate of other specified validated bacterial infections (see Table 12), and the number of hospitalizations secondary to all validated infectious complications were also studied (see Table 11 and Table 12).

Table 12.
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

None of the 61 treated subjects were positive for HCV, HIV-1, and HIV-2 and HBV prior to study entry and none converted from negative to positive during the 12-month period.

PI: SUBCUTANEOUS (SC) ADMINISTRATION

A prospective, open-label, non-controlled, multi-center study was conducted in the US to determine the efficacy, tolerability and PK of GAMMAGARD LIQUID subcutaneous infusion in 49 adult and pediatric subjects with PID. All subjects were treated for 12 weeks with GAMMAGARD LIQUID intravenous infusion every 3 or 4 weeks. Subjects who were on intravenous treatment prior to entering the study were switched to GAMMAGARD LIQUID at the same dose and frequency. Subjects who were receiving subcutaneous immune globulin were switched to GAMMAGARD LIQUID at the intravenous dose they had been given prior to switching to subcutaneous treatment. A PK analysis was performed at the end of the intravenous period in all subjects aged 12 years and older.

One week after the last intravenous infusion, each subject began subcutaneous treatment with GAMMAGARD LIQUID at 130% of the weekly equivalent of the intravenous dose for a minimum of 12 weeks. PK data from the first 15 adult subjects were used to determine the dose required to ensure that the IgG exposure with subcutaneous treatment was not inferior to that with intravenous treatment. The median dose determined from these subjects was 137% of the intravenous dose, and subsequently all subjects were treated for a minimum of 6 weeks at this dose. After 6 subcutaneous infusions, a trough IgG level was obtained and used to individually adapt the subcutaneous dose of GAMMAGARD LIQUID to compensate for individual variation from the mean value of 137% (see *Pharmacokinetics (12.3)* and *Dosage and Administration (2.1)]*. All subjects received a minimum of 12 infusions at this individually adapted dose. All subjects continued to receive subcutaneous treatment with GAMMAGARD LIQUID until the last subject completed the study. There were 47 subjects treated with 2,294 subcutaneous infusions of GAMMAGARD LIQUID: 4 subjects treated for up to 29 weeks, 17 subjects for 30 to 52 weeks, and 26 subjects for 53 weeks or longer. The median duration of subcutaneous treatment was 379 days (range: 57 to 477 days).

Efficacy was determined throughout the entire subcutaneous phase. There were 31 adults 16 years or older, 4 adolescents between 12 and <16 years of age, and 14 children between 2 years and <12. The volume of GAMMAGARD LIQUID infused was 30 mL per site for patients weighing 40 kg and greater, and 20 mL per site for those weighing less than 40 kg. The total weekly dose was divided by those values to determine the number of sites.

Mean weekly subcutaneous doses ranged from 181.9 milligram/kg to 190.7 milligram/kg (at 130% to 137% of the intravenous dose). In the study, the number of infusion sites per infusion was dependent on the dose of IgG and ranged from 2 to 10. In 75% of infusions, the number of infusion sites was 5 or fewer.

There were 3 serious validated bacterial infections, all bacterial pneumonia. None of these subjects required hospitalization to treat their infection. The annual rate of acute serious bacterial infections while on GAMMAGARD LIQUID subcutaneous treatment was 0.067, with an upper 99% confidence limit of 0.133, which is lower than the minimal goal of achieving a rate of <1 bacterial infection per patient-year.

The summary of infections and associated events for subjects during subcutaneous treatment with GAMMAGARD LIQUID is summarized in Table 13. The annual rate of any infection in this study during subcutaneous treatment, including viral and fungal infections, was 4.1 infections per subject per year.

Table 13.
Summary of Infections and Associated Events

Number of subjects (efficacy phase)	47
Total number of subject years	44
Annual rate of any infections	4.1 (95% CI 3.2 to 5.1) infections/subject year
Antibiotic use[§] (prophylaxis or treatment)	
Number of subjects (%)	40 (85.1%)
Annual rate	50.2 (95% CI 33.4 to 71.9) days/subject year
Days out of work/school/day care or unable to perform normal activities	
Number of subjects (%)	25 (53.2%)
Annual rate	4.0 (95% CI 2.5 to 6.1) days/subject year
Hospitalizations due to infections	
Number of subjects (%)	0 (0.0%)
Annual rate	0.0 (95% CI 0.0 to 0.1) days/subject year

[§] Included systemic and topical antibacterial, anti-fungal, anti-viral, and anti-protozoal antimicrobials.

MMN:

A randomized withdrawal, double-blind, placebo controlled, cross-over study was conducted to evaluate the efficacy and safety/tolerability of GAMMAGARD LIQUID in 44 adult subjects with MMN. The study examined grip strength in the more affected hand[13] (measured with dynamometer), and Guy's Neurological Disability Scale (GNDS) [upper limb part 6 subsection][14]. Study subjects were on a regimen of licensed Immunoglobulin (existing maintenance dose ranging from 0.5 to 2.0 grams/kg/month) prior to enrollment. The clinical trial was an enrichment design, therefore the results cannot be generalized to naïve patients. Each subject completed a five part, 12-week study parts (3 stabilization phases, one randomized withdrawal and one cross-over period). Open-label GAMMAGARD LIQUID was administered for 12 weeks at the beginning and end of the study for clinical stabilization, and between the double-blinded periods to prevent carry-over effect. If, during either of the double-blinded treatment period, the subject's upper limb function involving the affected muscles deteriorated, such that the subject had difficulty completing daily activities or the subject experienced a decline in grip strength of ≥50% in the more affected hand, the subject was switched directly to the next stabilization phase of open-label GAMMAGARD LIQUID ("accelerated switch") without breaking the blind.

All subjects were treated for 12 weeks with GAMMAGARD LIQUID during the initial stabilization (Stabilization-1) phase. In the cross-over 1 period, each subject was then randomized to either withdrawal from GAMMAGARD LIQUID to placebo or continue GAMMAGARD LIQUID for a period of 12 weeks and then transferred to stabilization phase 2. Subjects that did not tolerate the treatment during the double-blind cross-over period

were immediately transferred to open label GAMMAGARD LIQUID stabilization phase 2. Following Stabilization phase 2, the subjects were assigned to a second double-blind treatment for 12 weeks to either placebo or GAMMAGARD LIQUID depending on randomization received in cross-over period 1. No subject was allowed to experience placebo more than one time during the clinical study. Following this period the subjects were further stabilized for 12 weeks on open-label GAMMAGARD LIQUID, stabilization phase 3.

Sixty nine percent (n=29) required an accelerated switch to open-label treatment with GAMMAGARD LIQUID during the placebo period due to functional deterioration, but did not switch when receiving GAMMAGARD LIQUID. The median treatment days for treatment with GAMMAGARD LIQUID was 84 days and the median treatment days for the placebo was 28 days. Only one subject (2.4%) switched to open-label treatment during blinded GAMMAGARD LIQUID cross-over period 1 but did not switch during placebo administration ($p < 0.001$).

Forty-four subjects were evaluated to demonstrate effectiveness of GAMMAGARD LIQUID to improve or maintain muscle strength and functional ability in patients with MMN.

Statistical significance in favor of GAMMAGARD LIQUID over placebo was demonstrated by a substantially lower decline from baseline (22.30%; 95% CI: 9.92% to 34.67%) in the mean grip strength in the more affected hand following treatment (see Table 14). The difference in relative change for GAMMAGARD LIQUID and placebo of 22.94% (95% CI: 10.69 to 35.19) was statistically significant ($p < 0.001$).

Table 14.

Relative Change in Grip Strength in the More Affected Hand during Cross-over Period (ANOVA) (mIntent-to-Treat Dataset)

No. of subjects (N=41)

Statistics	Sequence 1		Sequence 2		Difference
	GAMMAGARD LIQUID	Placebo	Placebo	GAMMAGARD LIQUID	(GAMMAGARD LIQUID – Placebo)
N	22	22	19	20*	41
Mean (SD)	-16.36 (32.84)	-30.52 (29.68)	-29.19 (39.95)	1.46 (10.72)	22.30 (39.21)
Median	-3.90	-27.00	-25.03	-0.11	26.6

* A single subject in sequence 2, who was considered an outlier, was excluded from analysis.

Guy's Neurological Disability Scores (GNDS)[14] for the upper limbs, reflecting both fine motor skills and proximal strength, showed a significant difference in efficacy between GAMMAGARD LIQUID and placebo at the 2.5% level in favor of GAMMAGARD LIQUID. GNDS is a patient orientated clinical disability scale designed for multiple sclerosis and is considered appropriate for other neurological disorders.

As determined by GNDS scores for the upper limbs, 35.7% of subjects deteriorated while receiving the placebo, but not during treatment with GAMMAGARD LIQUID whereas 11.9% of subjects deteriorated during GAMMAGARD LIQUID but not over the placebo period. This difference was statistically significant ($p=0.021$) (see Table 15). 4.8% of subjects showed deterioration with both placebo and GAMMAGARD LIQUID, while 47.6% showed no deterioration on either.

Table 15.
McNemar's Test for Subjects with Deterioration in Guy's Neurological Disability Score (Intent-to-Treat Dataset)
No. of subjects (N=42)

Deterioration on Placebo	15 (35.7%)
Deterioration on GAMMAGARD LIQUID	5 (11.9%)
Deterioration on both	2 (4.8%)
No deterioration	20 (47.6%)

When data from both treatment sequences were combined, a relative decline of ≥30% in grip strength in the more affected hand occurred in 42.9% of subjects during the placebo period, but not during treatment with GAMMAGARD LIQUID. 4.8% of subjects experienced a ≥30% decline during treatment with GAMMAGARD LIQUID, but not during placebo. A relative decline of ≥30% in grip strength in the less affected hand occurred in 31.0% of subjects during the placebo period, but not during treatment with GAMMAGARD LIQUID. No subject experienced a ≥30% decline during treatment with GAMMAGARD LIQUID.

The Overall Disability Sum Score (ODSS) changed by -7.14% during placebo (indicating worsening of disability), and by -1.11% (indicating minimal change in disability) during treatment with GAMMAGARD LIQUID. For this specific analysis of ODSS, lower scores represented more disability.

With the dominant hand, subjects required 17% longer to complete the 9-hole peg test (a measure of dexterity) at the end of the placebo period compared to baseline. By contrast, at the end of the GAMMAGARD LIQUID treatment period, subjects required 1.2% longer to complete the 9-hole peg test for the dominant hand compared to baseline. With the non-dominant hand, subjects required 33% longer to complete the 9-hole peg test at the end of the placebo period and 6.7% longer at the end of the GAMMAGARD LIQUID treatment period compared to baseline.

Compared to baseline, patients' assessment of physical functioning, as measured by visual analog scale (VAS), showed a mean change of 290% during placebo compared to baseline. Patient's assessments of physical functioning showed a mean change of 73% during GAMMAGARD LIQUID treatment. Higher visual analog scale scores represent more severe disability.

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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 not made with natural rubber latex.

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.**
- Store GAMMAGARD LIQUID in the refrigerator or at room temperature.
- **Refrigeration:** 2° to 8°C [36° to 46°F] for up to 36 months.
- **Room Temperature:** up to 25°C [77°F] for up to 24 months.
- Expiration dates for both storage conditions are printed on the outer carton and vial label.
- Do not use past the applicable expiration date.

17 PATIENT COUNSELING INFORMATION

See FDA approved patient labeling (Information for Patients and Instructions for Use for PI patients only).

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*)*].
- Instruct patients to immediately report symptoms of thrombosis. These symptoms may include pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body. [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*)*].
- Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine (see *Warnings and Precautions (*5.6*)*].
- 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 (*5.7*)*].

Prior to starting GAMMAGARD LIQUID ask about a history of IgA deficiency, allergic reactions to immune globulin or other blood products. Patients with a history of allergic reactions should not be treated subcutaneously at home until several treatments have been administered and tolerated under medical supervision.

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)*].

SUBCUTANEOUS (SC) ADMINISTRATION ONLY

Self-administration—If self-administration is deemed to be appropriate by the physician, clear instructions and training on subcutaneous infusion should be given to the patient/caregiver, and the demonstration of their ability to independently administer subcutaneous infusions should be documented.

- Ensure the patient understands the importance of *consistent* weekly subcutaneous infusion to maintain appropriate steady IgG levels.
- Instruct the patient to keep a treatment diary/log book. This diary/log book should include information about each infusion such as, the time, date, dose, lot number(s) and any reactions.
- Inform the patient that mild to moderate local infusion-site reactions (e.g., swelling and redness) are a common side effect of subcutaneous treatment, but to contact their healthcare professional if a local reaction increases in severity or persists for more than a few days.

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

For Intravenous and Subcutaneous Administration

Information for Patients

The following summarizes important information about GAMMAGARD LIQUID. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about GAMMAGARD LIQUID. If you have any questions after reading this, ask your healthcare provider.

What is the most important information I need to know about GAMMAGARD LIQUID?

GAMMAGARD LIQUID can cause the following serious reactions:

- Severe allergic reactions causing difficulty in breathing or skin rashes
- Decreased kidney function or kidney failure
- Blood clots in the heart, brain, lungs or elsewhere in the body
- Severe headache, drowsiness, fever, painful eye movements, or nausea and vomiting
- Dark colored urine, swelling, fatigue, or difficulty breathing

What is GAMMAGARD LIQUID?

GAMMAGARD LIQUID is a ready-to-use, liquid medicine that contains immunoglobulin G (IgG) antibodies, which protect the body against infection. GAMMAGARD LIQUID is used to treat patients with primary immunodeficiency diseases (PI) and patients with multifocal motor neuropathy (MMN).

There are many forms of PI. The most common types of PI result in an inability to make a very important type of protein called antibodies, which help the body fight off infections from bacteria or viruses. GAMMAGARD LIQUID is made from human plasma that is donated by healthy people. GAMMAGARD LIQUID contains antibodies collected from these healthy people that replace the missing antibodies in PI patients.

MMN is a rare disease that causes muscle weakness that worsens over time. It affects the strength of the lower parts of arms and hands more than the legs, usually without affecting the touch sensation.

Who should not use GAMMAGARD LIQUID?

Do not use GAMMAGARD LIQUID if you have a known history of a severe allergic reaction to immune globulin or other blood products. If you have such a history, discuss this with your healthcare provider to determine if GAMMAGARD LIQUID can be given to you. Tell your healthcare provider if you have a condition called selective (or severe) immunoglobulin A (IgA) deficiency.

How should I use GAMMAGARD LIQUID?

GAMMAGARD LIQUID is given into a vein (intravenously) or under the skin (subcutaneously). For patients with PI, infusions into the vein are usually given every 3 or 4 weeks whereas infusions under the skin are given every week. For patients with MMN, infusions are given into a vein every 2 to 4 weeks as ordered by your physician. You and your healthcare provider will decide which way is best for you. Most of the time infusions under the skin are given at home by patients or caregivers. Although it is possible to give yourself infusions into the vein at home they are more often given in a hospital or infusion center by a nurse.

Instructions for giving GAMMAGARD LIQUID under the skin (subcutaneously) are provided in the Instructions for Use brochure. Only use GAMMAGARD LIQUID by yourself after you have been instructed by your healthcare provider.

What should I avoid while taking GAMMAGARD LIQUID?

GAMMAGARD LIQUID can make vaccines (like measles/mumps/rubella or chickenpox vaccines) not work as well for you. Before you get any vaccines, tell your healthcare provider that you take GAMMAGARD LIQUID.

Tell your healthcare provider if you are pregnant, or plan to become pregnant, or if you are nursing.

What are the possible or reasonably likely side effects of GAMMAGARD LIQUID?

The following one or more possible reactions may occur at the site of infusion. These generally go away within a few hours, and are less likely after the first few infusions.

- Mild or moderate pain
- Swelling
- Itching
- Redness
- Bruising
- Warmth

During the infusion of GAMMAGARD LIQUID, look out for the first signs of the following common side effects:

- Headache
- Migraine
- Fever
- Fatigue
- Itching
- Rash/Hives
- Cough
- Chest pain/tightness
- Chills/Shaking chills
- Dizziness
- Nausea/Vomiting
- Faster Heart Rate
- Upper Abdominal Pain
- Increased Blood Pressure
- Muscle cramps
- Sore throat

If any of the following problems occur after starting treatment with GAMMAGARD LIQUID, stop the infusion immediately and contact your healthcare provider or call emergency services. These could be signs of a serious problem.

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of irritation of the lining around your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver problem or a blood problem.
- Chest pain or trouble breathing, or blue lips or extremities. These could be signs of a serious heart or lung problem.
- Fever over 100°F. This could be a sign of an infection.

These are not all of the possible side effects with GAMMAGARD LIQUID. You can ask your healthcare provider for physician's information leaflet. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Whenever giving yourself treatments at home, you should have another responsible person present to help treat side effects or get help if you have a serious adverse reaction occur. Ask your healthcare provider whether you should have rescue medications, such as antihistamines or epinephrine.

How do I store GAMMAGARD LIQUID?

Store vials in their original boxes to protect from light. Do not freeze GAMMAGARD LIQUID.

You can store GAMMAGARD LIQUID in the refrigerator or at room temperature. The maximum storage time for GAMMAGARD LIQUID depends on the storage temperature you choose.

In the Refrigerator: at 2° to 8°C (36° to 46°F) for up to 36 months.

Room Temperature: up to 25°C (77°F) for up to 24 months.

The refrigerator and room temperature expiration dates are printed on the vial labels and the box. Always check the expiration date. You should not use the product after the expiration date.

Note: If you remove GAMMAGARD LIQUID from the refrigerator and store it at room temperature, do not refrigerate again.

Resources at Baxter Available to the Patients:

For more information on patient resources, education, or insurance assistance please visit www.immunedisease.com.

Detailed Instructions for Subcutaneous Administration for Patients with PI ONLY

Do not begin subcutaneous treatment with GAMMAGARD LIQUID until you have received instructions as detailed above and are comfortable that you can perform all the steps on your own.

1. **If refrigerated, remove GAMMAGARD LIQUID from refrigerator—**remove the product box from the refrigerator and take the vial out of the box.

   Allow vials to reach room temperature. This may take up to 60 minutes.

   Do not heat up the product or shake the product.

   If stored at room temperature, take the vial out of the box.

   Check:

   - Expiration date. Do not use beyond expiration date.
   - Vial to see if it is clear and colorless to light yellow. If it is cloudy or has particles, do not use.
   - Protective cap is on the vial. Do not use the product if it does not have the cap.

   Repeat this step with as many boxes of GAMMAGARD LIQUID as necessary.

2. **Gather all supplies—**Collect all the items you will need for the infusion: vial(s) of GAMMAGARD LIQUID, infusion supplies (needle sets, transfer needles, alcohol swabs, syringes, gauze, and tape), sharps container, infusion pump, and treatment logbook.

3. **Prepare a clean work area—**Clean a work area with an antibacterial cleaner and place all gathered items on the clean surface. Find a quiet work area with as few distractions as possible.

4. **Wash hands—**Wash your hands thoroughly. Put on clean gloves if your health care provider has instructed you to wear them.

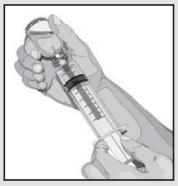
5. **GAMMAGARD LIQUID preparation—**If GAMMAGARD LIQUID is received in a bag or syringe, skip to step 7.

   Remove the cap from the vial. Wipe the vial stopper with an alcohol swab and allow to air dry (at least 30 seconds).

6. **Fill syringe from GAMMAGARD LIQUID vial(s)—**Remove sterile syringe from package and attach to a sterile needle. Pull back on plunger of the syringe to fill it with air, which should equal the amount of liquid you will be taking from the vial. Insert needle into the center of the vial stopper. Inject air into the vial and withdraw GAMMAGARD LIQUID into the syringe. (Example: If withdrawing 50 mL of GAMMAGARD LIQUID, inject 50 mL of air into the vial).

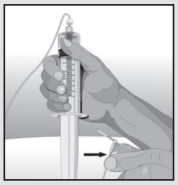
   If multiple vials are required to achieve the desired dose, repeat this step.

   If using a vented spike, it is not necessary to inject air into the vial with the syringe. Attach a sterile syringe to the spike, insert the spike into the center of the stopper, and pull back on the plunger to withdraw the desired volume.



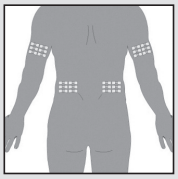
7. **Prepare the infusion pump and tubing—**If using a syringe driver pump, attach the syringe filled with GAMMAGARD LIQUID to the needle set. On a hard surface, gently push down on the plunger to fill (prime) the pump tubing up to the needle hub. This will ensure that no air is left in the tubing and needle (see picture).

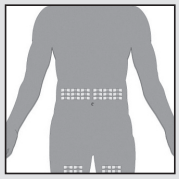
   If using a portable pump with GAMMAGARD LIQUID in a bag, follow manufacturer's instructions for preparing the pump and administration tubing, if needed.



8. **Select the infusion sites—**Select the number of infusion sites based on the volume of the total dose. It is recommended that you not inject more than 20 mL for children and 30 mL for adults into each infusion site.

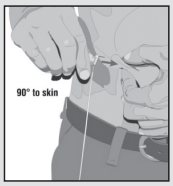
   See figure for potential locations of infusion sites (e.g., upper arms, abdomen, thighs, and lower back). Make sure sites are at least 2 inches apart. Avoid bony areas, visible blood vessels, scars and areas of inflammation (irritation) or infection.



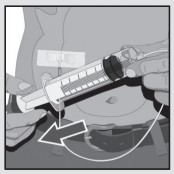


9. **Clean the infusion site(s)—**Clean the infusion site(s) with an alcohol swab. Allow to dry (at least 30 seconds).

10. **Insert the needle—**Remove the needle cover. Firmly grasp skin and pinch at least one inch of skin between two fingers. Insert needle with a rapid motion straight into the skin at a 90 degree angle. Tape the needle in place. Repeat this step for each infusion site.

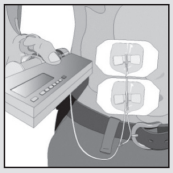


11. **Check for proper needle placement—**Before starting the infusion, check each needle for correct placement by gently pulling back on the attached syringe plunger and looking for any blood in the needle tubing. If you see any blood, remove and throw away the needle into the sharps container. Repeat filling (priming) and needle insertion steps in a different infusion site with a new needle.



12. **Secure the needle to the skin and start infusion—**Secure the needle(s) in place by putting a sterile clear bandage over the needle.

    Follow the manufacturer's instructions to turn pump on. Check infusion sites occasionally throughout the infusion.



13. **Remove needle set—**After the infusion is complete, remove the needle set by pulling it straight out. Gently press a small piece of gauze over the needle site and cover with a protective dressing.

    Throw away any unused product in the vial and the disposable supplies into the sharps container. Dispose of the sharps container using instructions provided with the container, or contact your healthcare provider.

14. **Record the infusion—**Remove the peel-off label from GAMMAGARD LIQUID vial, which has the product lot number and expiration date, and place the label in your treatment diary/log book. Write down the date, time, dose, and any reactions after each infusion.

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