GAMMAGARD LIQUID

[Immune Globulin Infusion (Human)] 10%

Tolerability Profile and Infusion Rates of Intravenous Administration of GAMMAGARD LIQUID

GAMMAGARD LIQUID The most utilized IgG brand in the United States[1a]

[a]Based on the most recent Marketing Research Bureau reporting published in November 2019 for sales in 2018.

Formulated with patients' needs in mind[2]

Designed for ease of use[2]

INDICATIONS

GAMMAGARD LIQUID is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients ≥2 years and as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).

IMPORTANT SAFETY INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin (IG) 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.**
- **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.**

Please see additional Important Safety Information throughout and click for Full Prescribing Information.

Formulated with patients' needs in mind[2]

- Stabilized and buffered with glycine[2] for those patients in whom additives may be a concern
- Osmolality (240-300 mOsmol/kg) similar to physiological osmolality[2]
- The packaging of this product is not made with natural rubber latex[2]

NO
added sugars[2,3]
added sodium[2,3]
added preservatives[2,3]
proline or glucose stabilizers[2]

Designed for ease of use

- Broad vial size selection: 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), and 30 g (300 mL)[2]
- Using a 30 g vial may help reduce the number of vials required and reduce the need for handling[4]
  - In a retrospective analysis of IVIG[a] pharmacy claims (n=1349)[b]
    - 55% of patients received a dose of 30 g or higher[4]
    - 30 g was the most frequently prescribed dose (nearly 1 in 5)[4]
    - For patients receiving greater than 30 g, with a 30 g vial[b]
      - 47% reduction in the number of vials needed[4]
      - 97% of all prescriptions dispensed with 3 or fewer vials[4c]
- Shelf life that allows up to 24 months at room temperature (up to 25°C [77°F]) and up to 36 months when refrigerated (2°C to 8°C [36° to 46°F])[d]; do not freeze[2]

[a]Intravenous immune globulin.
[b]Based on a 2010 analysis of 1,354 patients with PI representing 11,620 dispensing records.
[c]Compared with 70% of prescriptions dispensed prior to the introduction of the 30 g vial.
[d]After product has been removed from refrigerator and stored at room temperature, do not refrigerate again.[2]

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

- History of anaphylactic or severe systemic hypersensitivity reactions to human IG
- IgA-deficient patients with antibodies to IgA and a history of hypersensitivity to human IG. Anaphylaxis has been reported with intravenous (IV) use of GAMMAGARD LIQUID.

Warnings and Precautions

Hypersensitivity: Severe hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human IG. If a hypersensitivity reaction occurs, discontinue infusion immediately and institute appropriate treatment. IgA-deficient patients with antibodies to IgA are at greater risk of developing potentially severe hypersensitivity reactions, including anaphylaxis.

Renal Dysfunction/Failure: Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis, and death may occur with IV use of IG products, especially those containing sucrose. Ensure patients are not volume depleted prior to infusion. In patients at risk due to pre-existing renal insufficiency or predisposition to acute renal failure, assess renal function before initiation and throughout treatment, and use the minimum infusion rate practicable for IV administration. If renal function deteriorates, consider discontinuation.

Please see additional Important Safety Information throughout and click for Full Prescribing Information, including Boxed Warning regarding Thrombosis, Renal Dysfunction and Acute Renal Failure.

IV Dosing and Infusion Rates of GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10% Solution

Primary Immunodeficiency (PI) Patients

Dose: 300 to 600 mg/kg every 3 to 4 weeks based on clinical response[2,3a]

Initial Infusion Rate: 0.5 mL/kg/hr (0.8 mg/kg/min) for 30 minutes[2]

Maintenance Infusion Rate: Increase every 30 minutes (if tolerated) up to 5.0 mL/kg/hr (8 mg/kg/min)[2,3]

In a clinical study for GAMMAGARD LIQUID IV administration for PI (N=61)[3]:
The mean infusion rate achieved by all subjects treated for PI was 4.3 mL/kg/hr.[3]

- 58 (95%) subjects achieved a maximum infusion rate of 4.0 mL/kg/hr or greater[3b]
  - Of these subjects, 16 (26%) subjects attained a rate of 5.0 mL/kg/hr[3]

[a]Adjust dose according to IgG levels and clinical response, as the frequency and dose of immune globulin may vary from patient to patient.[2]
[b]Infusion rates were adjusted based on the patient's clinical response.

Multifocal Motor Neuropathy (MMN) Patients

Dose: 0.5 to 2.4 g/kg every month based on clinical response[2c,d,e]

Initial Infusion Rate: 0.5 mL/kg/hr (0.8 mg/kg/min)[2]

Maintenance Infusion Rate: Infusion rate may be increased (if tolerated) to a maximum rate of 5.4 mL/kg/hr (9 mg/kg/min)[2]

In a clinical study for GAMMAGARD LIQUID IV administration for MMN, the largest clinical study in MMN to date (N=44)[2,6f]:
The median dose achieved per subject treated for MMN was 1.2 g/kg/mo (range 0.5 to 2.4).[2,6]

[c]Dose may need to be adjusted to achieve the desired clinical response. 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. This is not intended to recommend a specific treatment for any particular patient group or provide medical advice.
[d]As initial dose was not studied, dosing guidance is available from existing EFNS/PNS guidelines.[5]
[e]Each 12-week study part comprised 3, 4, or 6 infusion cycles, depending on treatment intervals (2, 3, or 4 weeks).[6]

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur. It is critical to distinguish true hyponatremia from a pseudohyponatremia because certain treatments may lead to volume depletion, a further increase in serum viscosity, and a predisposition to thromboembolic events.

Thrombosis: May occur following treatment with IG products and in the absence of known risk factors. In patients at risk, administer at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Aseptic Meningitis Syndrome: Has been reported with use of IG and may occur more frequently in females. Conduct a thorough neurological exam on patients exhibiting signs and symptoms, to rule out other causes of meningitis. Discontinuing IG treatment has resulted in remission within several days without sequelae.

Hemolysis: GAMMAGARD LIQUID contains blood group antibodies, which may cause a positive direct antiglobulin reaction and hemolysis. Monitor patients for signs and symptoms of hemolysis and delayed hemolytic anemia and, if present, perform appropriate confirmatory lab testing.

Please see additional Important Safety Information throughout and click for Full Prescribing Information, including Boxed Warning regarding Thrombosis, Renal Dysfunction and Acute Renal Failure.

The demonstrated tolerability of IV administration of GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10% Solution was established in a clinical trial for PI (N=61)

Adverse reactions[a] in patients with PI

Fifteen adverse reactions in 8 subjects were serious. Of these, 2 serious reactions (2 episodes of aseptic meningitis in 1 patient) were deemed to be possibly related to the infusion of GAMMAGARD LIQUID.[2]

Adverse Reactions Occurring in ≥5% of Subjects With PI[2]

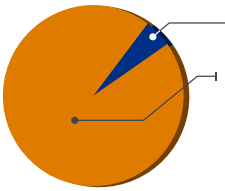
Event	By Infusion N (%) (N=1812 Infusions)	By Subject N (%) (N=61 Subjects)
Headache	94 (5.2%)	29 (47.5%)
Fatigue	33 (1.8%)	14 (23.0%)
Pyrexia	28 (1.5%)	17 (27.9%)
Nausea	17 (0.9%)	11 (18.0%)
Chills	14 (0.8%)	8 (13.1%)
Rigors	14 (0.8%)	8 (13.1%)
Pain in extremity	13 (0.7%)	7 (11.5%)
Diarrhea	12 (0.7%)	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%)

5.2%
rate of headache per infusion[2b]
(94 of 1812 infusions)

In the study, of the 400 nonserious adverse reactions:

- 217 were mild[2c]
- 164 were moderate[2d]
- 19 were severe[2e]

Participation in the 12-month clinical study



5% of patients discontinued study participation before 12 months of treatment for any reason[3]

95% of patients completed 12 months of treatment with GAMMAGARD LIQUID in the clinical study[3]

N=61

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.[2,7]

[a] Adverse reaction is defined as an adverse event occurring during or within 72 hours of infusion or any causally related event occurring within the study period.
[b] The most common systemic adverse reaction per infusion.
[c] Transient discomfort that resolves spontaneously or with minimal intervention.
[d] Limited impairment of function and resolves spontaneously or with minimal intervention and no sequelae.
[e] Marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae.

IMPORTANT SAFETY INFORMATION (continued)

Warnings and Precautions (continued)

Transfusion-Related Acute Lung Injury: Non-cardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil and anti-HLA antibodies in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Transmittable Infectious Agents: Because GAMMAGARD LIQUID is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, other pathogens). No confirmed cases of viral transmission or variant Creutzfeldt-Jakob disease (vCJD) have been associated with GAMMAGARD LIQUID.

Interference with Lab Tests: False positive serological test results and certain assay readings, with the potential for misleading interpretation, may occur as the result of passively transferred antibodies.

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The demonstrated tolerability profile of IV administration of GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10% Solution was established in a clinical study for MMN (N=44)

Adverse reactions[a] in adult patients with MMN[2]

Two serious adverse reactions in the clinical trial for MMN, each impacting 1 subject, were pulmonary embolism and blurred vision.[2]

Adverse Reactions Occurring in ≥5% of Subjects With MMN[2]

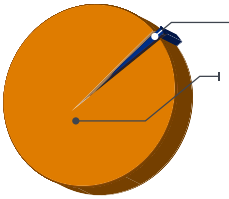
	GAMMAGARD LIQUID		Placebo	
Event	By Infusion N (%) (N=983 Infusions)	By Subject N (%) (N=44 Subjects)	By Infusion N (%) (N=129 Infusions)	By Subject N (%) (N=43 Subjects)
Headache	28 (2.85%)	14 (31.82%)	3 (2.33%)	2 (4.65%)
Chest discomfort	3 (0.31%)	3 (6.82%)	0 (0.00%)	0 (0.00%)
Muscle spasms	3 (0.31%)	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%)

2.9%
rate each of headache and nausea per infusion[2b] (28 of 983 infusions)

Among the 317 nonserious adverse events, 176 were considered adverse reactions.[2] Of these

- 126 were mild[2c]
- 37 were moderate[2d]
- 13 were severe[2e]

GAMMAGARD LIQUID infusion experiences[6]



1.65% of infusions required an interruption, reduction in rate, or discontinuation for any reason[f]

98.35% of infusions were completed without an interruption, reduction in rate, or discontinuation for any reason

n=242 infusions during the cross-over periods.

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[b] The most common systemic adverse reactions per infusion.
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[e] Marked impairment of function or can lead to temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae.
[f] Compared to 0.78% of infusions for placebo (N=129).[6]

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5g
10g
100mL
single-dose container
20g
200mL
LE-07-16356
NDC 0944-2700-07
Immune Globulin Infusion
(Human) 10%
GAMMAGARD LIQUID
Solution for Infusion
Refrigeration: 36 months storage at refrigerated temperature 2°-8°C (36°F-46°F). Do not freeze.
Room temperature: 12 months storage at room temperature 25°C (77°F) within the first 24 months from the date of manufacture.
See package insert for detailed storage information.

INDICATIONS

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Warnings and Precautions (continued)

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Transfusion-Related Acute Lung Injury: Non-cardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil and anti-HLA antibodies in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Transmittable Infectious Agents: Because GAMMAGARD LIQUID is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, other pathogens). No confirmed cases of viral transmission or variant Creutzfeldt-Jakob disease (vCJD) have been associated with GAMMAGARD LIQUID.

Interference with Lab Tests: False positive serological test results and certain assay readings, with the potential for misleading interpretation, may occur as the result of passively transferred antibodies.

Adverse Reactions

The most serious adverse reactions observed in clinical studies were aseptic meningitis, pulmonary embolism, and blurred vision.

The most common adverse reactions observed in ≥5% of subjects were:

IV administration for PI: 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 for PI: infusion site (local) event (rash, erythema, edema, hemorrhage, and irritation), 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.

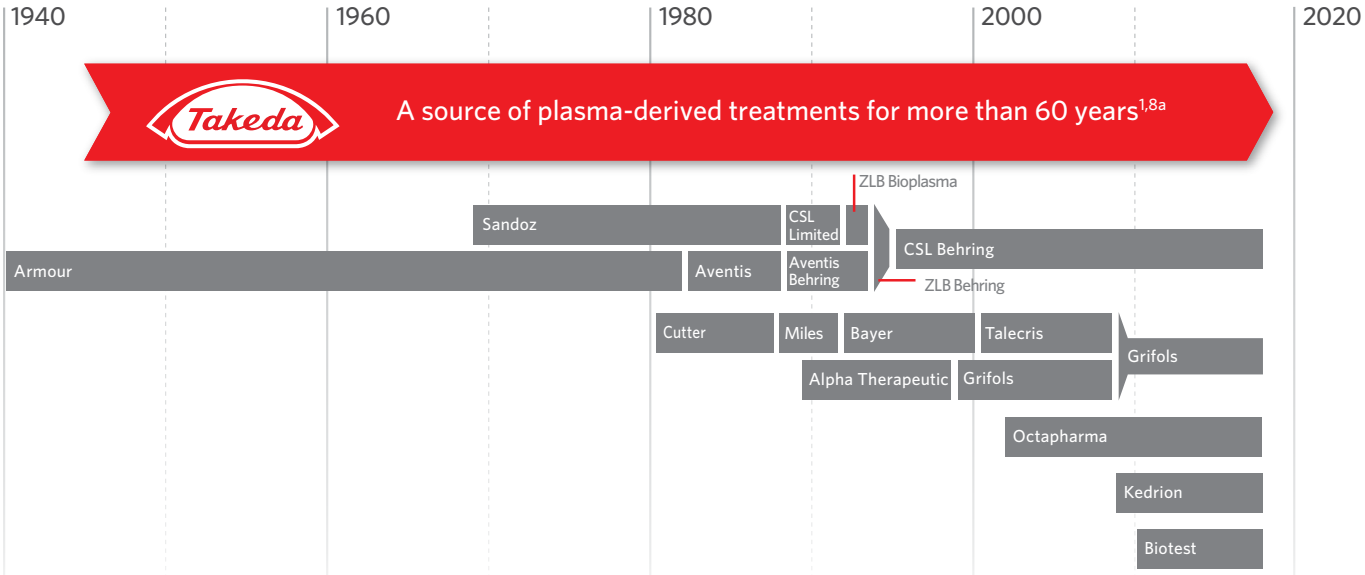
IV administration for MMN: headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity.

Drug Interactions

Passive transfer of antibodies may transiently interfere with immune responses to live attenuated virus vaccines (e.g., measles, mumps, rubella, and varicella).

Click for Full Prescribing Information.

A History of Leadership and a Commitment to the Future



- Demonstrated experience as an IgG supplier for more than 30 years.[1,8a]
- Takeda has invested more than $1 billion to build a new, state-of-the-art plasma fractionation facility in Covington, GA.[9,10]
- Takeda is committed to maintaining high standards of plasma safety.
- Takeda is focused on optimizing our global manufacturing operation.

[a]Includes combined years of product history from Baxter, Baxalta, and Shire.

Covington, GA

OVER $1 BILLION investment in state-of-the-art fractionation facility[9]

APPROXIMATELY 30% INCREASE IN internal plasma manufacturing network once fully operational[10]

One of the largest plasma collection networks in the United States[1]

References: 1. Marketing Research Bureau. The plasma proteins market in the United States 2018. Published November 2019. **2.** GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10% [prescribing information]. Westlake Village, CA: Baxalta US Inc. **3.** 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. **4.** Data on file. Analysis of potential vial reduction 30 g size. Baxter Healthcare Corporation. **5.** Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. *J Peripher Nerv Syst.* 2010;15(4):295-301. **6.** Data on file. GAMMAGARD LIQUID [Immune Globulin Infusion (Human)] 10%--final clinical study report. Baxalta US Inc. **7.** Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* 2005;94(5 Suppl 1):S1-S63. **8.** Center for Biologic Evaluation and Research. List of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations to date. https://www.fda.gov/media/89426/download. Accessed January 13, 2020. **9.** Baxter International Inc. 2012 Annual Report. **10.** Data on file. Takeda.

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