

PRODUCT MONOGRAPH

GAMMAGARD LIQUID[®]

Immunoglobulin Intravenous (Human), [IGIV] 10%

Solution for infusion and 1 g/10 mL, 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL,
30 g/300mL

Pharmacopeial

Replacement Therapy for Immunodeficiencies

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GAMMAGARD LIQUID

Immunoglobulin Intravenous (Human) 10%

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Solution for infusion 1.0 g/10 mL 2.5 g/25 mL 5.0 g/50 mL 10.0 g/100 mL 20.0 g/200 mL 30.0 g/300 mL	None of the nonmedicinal ingredients are clinically relevant. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

GAMMAGARD LIQUID is a purified IgG liquid biologic product at 10% w/v protein concentration. This preparation is an isotonic solution containing a concentration of approximately 100 mg of protein per mL, of which at least 98% is gamma globulin, and has a pH of 4.6 to 5.1^a. The stabilizing agent is glycine and is present in the amount of 0.25M (0.20 to 0.30M). The product contains no preservatives.

GAMMAGARD LIQUID is available in 6 pack sizes, i.e. 1 g in 10 mL, 2.5 g in 25 mL, 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL and 30 g in 300 mL solution. The product is filled into containers of type I glass, which are closed with bromobutyl rubber stoppers.

The GAMMAGARD LIQUID manufacturing process employs a modified Cohn-Oncley cold alcohol fractionation procedure to isolate an intermediate immunoglobulin G (IgG) fraction, referred to as Precipitate G, from frozen human plasma pools. Precipitate G is further purified by a continuous process through the use of weak cation exchange chromatography (CM Sepharose Fast Flow) and weak anion exchange chromatography (ANX Sepharose 4 Fast Flow, low substitution), to final formulation. Three dedicated virus reduction steps are included in the downstream purification of Precipitate G, which are solvent/detergent (S/D) treatment,

^a pH is measured after the solution is diluted to 1% protein with saline. The pH range of 4.6 to 5.1 corresponds to a range of 4.4 to 4.9 when the solution is measured undiluted. Measurement of the undiluted solution was performed during process and formulation development, and will be routinely performed in manufacturing to monitor the process.

nanofiltration, and incubation at low pH and elevated temperature in the final formulation. The final formulation step is achieved at the ultra/diafiltration step against 0.25M glycine buffer at pH 4.2 to meet the final release criteria of an osmolality of 240 to 300 mOsmol/kg, a pH of 4.6 to 5.1¹, and a protein concentration of human IgG of 9.0 to 11.0%.

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

GAMMAGARD LIQUID belongs to the pharmacotherapeutic group of immune sera and immunoglobulins, immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02. The active ingredient of GAMMAGARD LIQUID is human polyvalent IgG. The native structure and function of the IgG molecules are not compromised throughout the manufacturing process. Therefore, the product retains the subclass distribution and the broad spectrum of antibody specificities present in human plasma, and exerts all the critical biological activities of polyvalent antibody molecules. The exact mechanism of action other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

Intravenous immunoglobulins are indicated in primary immunodeficiency syndromes, and secondary antibody deficiencies such as in myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogammaglobulinemia, and in children with congenital AIDS or allogenic bone marrow transplantation. They are also recommended for immunomodulation in idiopathic thrombocytopenic purpura (ITP) and for the treatment of Multifocal Motor Neuropathy (MMN).

INDICATIONS AND CLINICAL USE

GAMMAGARD LIQUID is indicated for:

- **Primary immunodeficiency**

Replacement therapy in primary immunodeficiency syndromes (PID) such as:

- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Wiskott Aldrich syndrome

- **Secondary Immunodeficiency**

Replacement therapy in secondary immunodeficiency syndromes (SID) such as:

- B-cell chronic lymphocytic leukemia
- Pediatric HIV infection

- Allogeneic bone marrow transplantation

- **Idiopathic thrombocytopenic purpura (ITP)**

- **Multifocal Motor Neuropathy (MMN)**

- Maintenance therapy to improve muscle strength and disability in adult patients with MMN. GAMMAGARD LIQUID should be administered under the supervision of a qualified health professional who is experienced in the use of immunoglobulins and in the management of PID, SID and ITP. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Geriatrics and Pediatrics (>24 months of age):

Age inclusion criterion for Clinical Study No. 160101 was >24 months. However, no specific geriatric or pediatric studies were performed.

CONTRAINDICATIONS

GAMMAGARD LIQUID is contraindicated in patients with severe hypersensitivity responses to Immunoglobulin (Human).

Patients with severe IgA deficiency (IgA<0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis has been reported with the use of GAMMAGARD LIQUID even though it contains low amounts of IgA (≤ 0.14 mg per mL).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Immunoglobulin Intravenous (Human) products have been reported to be associated with

- renal dysfunction, including: acute tubular necrosis, proximal tubular nephropathy,
- acute renal failure (including GAMMAGARD LIQUID),
- osmotic nephrosis,
- thrombotic events and
- death.¹

Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

Thrombotic and thromboembolic events have been reported in association with IGIV treatment including myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins.

Thrombosis may occur even in the absence of known risk factors.

Risk factors for thromboembolic events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors. For further information please refer to WARNINGS and PRECAUTIONS- Thrombotic Events section.

GAMMAGARD LIQUID does not contain sucrose. Glycine, an amino acid, is used as a stabilizer.

The physician should discuss the risks and benefits of this product with the patient.

General

GAMMAGARD LIQUID is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the classic Creutzfeldt-Jakob disease agent. This also applies to unknown or emerging viruses and other pathogens. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. The measures taken (including solvent/detergent treatment, 35nm nanofiltration, and a low-pH incubation at elevated temperature 30-32°C) are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the nonenveloped viruses HAV and parvovirus B19. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Takeda Canada Inc.

GAMMAGARD LIQUID should only be administered intravenously. Immediate anaphylactic and hypersensitivity reactions are a remote possibility. Anaphylaxis has been reported with the use of GAMMAGARD LIQUID. Epinephrine and antihistamines should be available for treatment of any acute anaphylactoid reactions.

Hypersensitivity

Rarely, human normal immunoglobulin can induce an anaphylactic reaction with a fall in blood pressure, even in patients who had tolerated previous treatment with human normal immunoglobulin. Patients with antibodies to IgA or with IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IGIV therapy is indicated may be at increased risk of anaphylactic reaction.

GAMMAGARD LIQUID is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern (see CONTRAINDICATIONS). These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immunoglobulin is clearly indicated.

Renal Complications

Severe renal adverse reactions have been reported in patients receiving IGIV treatment, particularly those products containing sucrose. (PLEASE NOTE: GAMMAGARD LIQUID does not contain sucrose). These reactions include acute renal failure (including

GAMMAGARD LIQUID administered intravenously), acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.

Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Acute renal failure has been reported with GAMMAGARD LIQUID. Assure that patients are not volume depleted prior to the initiation of infusion of GAMMAGARD LIQUID. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of IGIV products and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk of developing renal dysfunction, it may be prudent to reduce the rate of infusion to less than 3.3 mg IgG/kg/min (<2 mL/kg/hr).

Haemolysis

IGIV products, including GAMMAGARD LIQUID, can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis.^{2,3,4} Haemolytic anemia can develop subsequent to IGIV therapy (including GAMMAGARD LIQUID) due to enhanced red blood cells (RBC) sequestration (see ADVERSE REACTIONS).⁵ IGIV recipients should be monitored for clinical signs and symptoms of haemolysis (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema (TRALI) in patients administered IGIV, including GAMMAGARD LIQUID.⁶ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever, and typically occurs within 1-6 hours after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Thrombotic Events

Thrombotic and thromboembolic events, including myocardial infarction, cerebral vascular accident, deep vein thrombosis and pulmonary embolism have been reported in association with

IGIV (including GAMMAGARD LIQUID administered intravenously) (see ADVERSE REACTIONS).^{7,8,9,10,11,12,13,14,15}

Patients at risk may include those with obesity, hypertension, history of atherosclerosis, history of vascular disease or thrombotic episodes, multiple cardiovascular risk factors, advanced age, impaired cardiac output, diabetes mellitus, acquired or inherited thrombophilic disorders and/or known or suspected hyperviscosity, hypercoagulable disorders, use of estrogens, indwelling central vascular catheters, severe hypovolemia and prolonged periods of immobilization.

The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. The drug product should be administered at the minimum dose available and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests). Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

Aseptic Meningitis Syndrome

Aseptic meningitis syndrome (AMS) has been reported to occur in association with IGIV treatment, including 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. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic mm, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in female patients.

Hyperproteinemia

Hyperproteinemia and increased serum viscosity may occur in patients received IGIV therapy. In addition, hyponatremia may occur in association with IGIV products. It is clinically critical to distinguish true hyponatremia from a pseudohyponatremia that is associated with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at

decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a possible predisposition to thromboembolic events.

Interference with Laboratory Tests

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

Administration of GAMMAGARD LIQUID can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

Special Populations

Pregnancy and Lactation:

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

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore it should only be given with caution to pregnant women and breast-feeding mothers.

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

Monitoring and Laboratory Tests

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

If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [see WARNINGS AND PRECAUTIONS].

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [see WARNINGS AND PRECAUTIONS].

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Various mild and moderate reactions, such as headache, fever, fatigue, chills, flushing, dizziness, urticaria, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, muscle cramps, and changes in blood pressure can occur with infusions of Immunoglobulin Intravenous (Human). In general, reported adverse reactions to GAMMAGARD LIQUID in patients with Primary Immunodeficiency are similar in kind and frequency to those observed with other IGIV products. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. Although hypersensitivity reactions have not been reported in the clinical studies with GAMMAGARD LIQUID immediate anaphylactic and hypersensitivity reactions are a remote possibility. Anaphylaxis has been reported with the use of GAMMAGARD LIQUID. Epinephrine and antihistamines should be available for treatment of any acute anaphylactic reactions [see WARNINGS AND PRECAUTIONS].

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis.

Clinical Trial Adverse Drug Reactions

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

Adverse reactions were pooled from three clinical trials, two Primary Immune Deficiency trials (160101 and 160001) and one Idiopathic Thrombocytopenic Purpura trial (160002), in which a total of 106 subjects were enrolled. Adverse reactions that occurred at a frequency greater than 1% are shown in Table I-1. All events were expected based on past experiences with

intravenous gammaglobulin products.

Table I-1: GAMMAGARD Clinical Trial Adverse Reactions for PID and ITP		
System Organ Class (SOC)	Preferred MedDRA Term	Frequency Percentage per Infusion
Nervous System Disorders	Migraine	1.36
	Headache	7.10
Gastrointestinal Disorders	Nausea	8.17
Skin and Subcutaneous Tissue Disorders	Urticaria	1.27
General Disorders and Administration Site Conditions	Fatigue	1.91
	Pyrexia	2.32
	Chills	1.27

During Study 160101, viral safety was assessed by serological screening for HBsAg and antibodies to HCV and HIV-1 and HIV-2 prior to, during, and at the end of the study and by Polymerase Chain Reaction (PCR) tests for HBV, HCV, and HIV-1 genomic sequences prior to and at the end of the study. None of the 61 treated subjects were positive prior to study entry and none converted from negative to positive during the 12-month period of study.

Adverse reactions from MMN clinical trial 160604 occurred at a frequency greater than 1% are shown in Table I-2.

Table I-2: GAMMAGARD Clinical Trial Adverse Reactions for MMN		
System Organ Class (SOC)	Preferred MedDRA Term	Frequency Percentage per Infusion
Nervous System Disorders	Headache	3.46
Vascular Disorders	Flushing	1.12
Gastrointestinal Disorders	Nausea	3.15
Musculoskeletal and Connective Tissue Disorders	Muscle spasms	1.22

One serious adverse event, pulmonary embolism, was reported in the MMN clinical trial (160604). Due to the low incidence of pulmonary embolism, it is not possible to come to any conclusions regarding risk factors by indication, dose, or individual patient characteristics.

Muscle twitching and weakness were reported only in patients with MMN, and myalgia and back pain were reported in higher incidence in the MMN population, and may also be related to their underlying neuromuscular condition.

Clinical Trial Adverse Drug Reactions for PID, ITP (<1)

Infections and Infestations: Meningitis aseptic

Blood and Lymphatic System Disorders: Lymphadenopathy, Anemia

Psychiatric Disorders: Anxiety, Insomnia

Nervous System Disorders: Amnesia, Dysarthria, Dizziness, Dysgeusia, Burning sensation

Eye Disorders: Eye swelling, Eye pain, Conjunctivitis

Ear and Labyrinth Disorders: Vertigo

Cardiac Disorders: Tachycardia

Vascular Disorders: Hypertension, Flushing, Phlebitis, Peripheral coldness

Respiratory, Thoracic, and Mediastinal Disorders: Cough, Oropharyngeal pain, Rhinorrhea, Oropharyngeal swelling, Asthma, Nasal congestion

Gastrointestinal Disorders: Diarrhea, Vomiting

Skin and Subcutaneous Tissue Disorders: Pruritus, Dermatitis, Rash erythematous, Angioedema, Cold sweat

Musculoskeletal and Connective Tissue Disorders: Pain in extremity, Back pain, Myalgia, Muscle spasms

General Disorders and Administration Site Conditions: Influenza like illness, Edema, Feeling hot, Infusion site pain, Infusion site phlebitis, Infusion site swelling, Application site pruritus, Infusion site reaction, Malaise

Investigations: Body temperature increased, Respiratory rate increased, White blood cell count decreased, Red blood cell count decreased, Hematocrit decreased, Blood urea increased, Blood creatinine increased, Blood cholesterol increased

Injury, Poisoning and Procedural Complications: Contusion

Clinical Trial Adverse Drug Reactions for MMN (<1%)

Psychiatric Disorders: Irritability

Nervous System Disorders: Migraine, Hypoesthesia, Paresthesia, Balance disorder

Cardiac Disorders: Sinus Tachycardia

Vascular Disorders: Flushing, Phlebitis, Hot flush

Respiratory, Thoracic, and Mediastinal Disorders: Oropharyngeal pain, Pulmonary embolism

Gastrointestinal Disorders: Diarrhea, Vomiting, Nausea

Skin and Subcutaneous Tissue Disorders: Rash erythematous, Night sweat, Photosensitivity reaction

Musculoskeletal and Connective Tissue Disorders: Pain in extremity, Back pain, Myalgia, Muscle spasms, Muscle twitching, Muscular weakness

Renal and Urinary Disorders: Proteinuria

General Disorders and Administration Site Conditions: Pyrexia, Influenza like illness, Peripheral edema, fatigue, Chills, Asthenia, chest discomfort, Infusion related reactions

Investigations: Blood pressure increased, Alanine aminotransferase increased.

Adverse Events

In addition to the adverse drug reactions noted above, the following adverse events were noted in the post-efficacy observation period in Study 160101: sinusitis, upper respiratory tract infection, acne, Herpes simplex, oral candidiasis.

Abnormal Hematologic and Clinical Chemistry Findings

Hematology and clinical chemistry parameters were monitored in all subjects in Study 160101 prior to each infusion throughout the 12-month period of study. Mean values for all laboratory parameters remained consistent throughout the study period. Three of the hematology values in one subject were outside of the normal range and reported as non-serious adverse experiences that resolved completely. These were a red cell count of $3.9 \times 10^6/\mu\text{L}$, hematocrit of 31%, and white cell count of $3.88 \times 10^3/\mu\text{L}$, all spontaneously returned to baseline. Using the International Grading System only one decrease of hemoglobin to Grade 2 (on a 0-4 scoring system) was observed, a value of 9.5 g/dL. There were several patients who had hemoglobin levels of Grade 1 (>10.0 g/dL) that were below the lower limits of normal. There were no decreases in hemoglobin that required further evaluation or intervention in any of the three clinical trials. One subject had an elevated BUN (45 mg/dL) and creatinine (1.4 mg/dL) on one occasion that were reported as non-serious adverse experiences and resolved completely. These values improved to 30 mg/dL and 0.8 mg/dL, respectively, by the next infusion. Six of the patients had a single, transient elevation in serum transaminases. Two additional patients had persistent elevations in transaminases, ALT and AST, which were present at the initiation of the study, prior to the infusion of GAMMAGARD LIQUID. There was no other evidence of liver abnormalities. None of the hematology or chemistry laboratory abnormalities that occurred during the course of the study required clinical intervention and none had clinical consequences.

Post-Market Adverse Drug Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by System

Order Class (SOC), then by Preferred MedDRA term in order of severity.

Blood and Lymphatic System Disorders: Haemolysis

Immune System Disorders: Anaphylactic shock, Anaphylactic reaction, Hypersensitivity

Nervous System Disorders: Stroke, Transient ischemic attack, Tremor

Vascular Disorders: Myocardial infarction, Deep vein thrombosis, Hypotension

Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, Pulmonary edema, Dyspnea

Gastrointestinal Disorders: Abdominal pain

Skin and Subcutaneous Tissue Disorders: Hyperhidrosis

General Disorders and Administration Site Conditions: Chest pain, Chills

Investigations: Coombs direct test positive, Oxygen saturation decreased

Injury, Poisoning and Procedural Complications: Transfusion related acute lung injury

DRUG INTERACTIONS

Overview

Antibodies in IGIV products may interfere with patient responses to live vaccines, such as those for measles, mumps, rubella and varicella.¹⁷ The immunizing physician should be informed of recent therapy with IGIV products so that appropriate precautions can be taken.

Admixtures of GAMMAGARD LIQUID with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMMAGARD LIQUID be administered separately from other drugs or medications that the patient may be receiving. Normal saline should not be used as a diluent. If dilution is preferred, GAMMAGARD LIQUID may be diluted with 5% dextrose in water.¹⁶ No other drug interactions or compatibilities have been evaluated.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dose and dosage regimen are dependent on the indication.

In replacement therapy the dosage may need to be individualized for each patient depending on the pharmacokinetic and clinical response. The dosage regimens are given as a guideline below.

In patients at risk for acute renal failure or thromboembolic adverse reactions, GAMMAGARD LIQUID should be administered at the lowest rate of infusion. Patients should be adequately hydrated before administration.

In general, it is recommended that patients beginning therapy or switching from one intravenous immunoglobulin brand to another be started at the lowest rate and then advanced to the maximal rate if they have tolerated several infusions at intermediate rates of infusion.

GAMMAGARD LIQUID should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Only clear slightly opalescent and colorless or pale yellow solutions are to be administered.

Recommended Dose and Dosage Adjustment

GAMMAGARD LIQUID is intended for intravenous administration. Dosage will vary depending on condition and bodyweight. The following doses are in agreement with currently suggested dosing schedules ¹⁷:

Table I-3 Recommended Dose and Dosage Adjustment		
Indication	Dose	Frequency of Injections
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 – 0.8 g/kg BW - thereafter: 0.2 – 0.8 g/kg BW	every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L
Replacement therapy in secondary immunodeficiency Allogeneic bone marrow Transplantation Treatment of infections and prophylaxis of graft-versus host disease Persistent lack of antibody production	0.2 – 0.4 g/kg BW 0.5 g/kg 0.5 g/kg	every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L every week from day -7 up to 3 months after transplantation every month until antibody levels return to normal
Idiopathic thrombocytopenic purpura	0.8 – 1 g/kg BW or 0.4 g/kg BW/d	on day 1, possibly repeated once within 3 days for 2 – 5 days
Multifocal Motor Neuropathy (MMN)	0.5 – 2.4g/kg	every month based on clinical response

Missed Dose

Give product at the earliest available opportunity.

Administration

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 mL/kg BW/hr for 30 minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 8 mL/kg BW/hr. In patients at risk for acute renal failure or thromboembolic adverse reactions, GAMMAGARD LIQUID should not be administered at the maximum allowable rate of infusion.

For treatment of Multifocal Motor Neuropathy (MMN), Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 mL/kg BW/hr. If well tolerated, the rate of administration may gradually be increased to a maximum rate of 5.4 mL/kg BW/hr. Certain adverse reactions such as headaches and flushing may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. The infusion may then be resumed at a rate that does not result in recurrence of the symptoms. (See ADVERSE REACTIONS)

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

GAMMAGARD LIQUID is recommended for infusion at a concentration of 10%. Do not use normal saline as a diluent. If it must be diluted, 5% dextrose in water should be used as a diluent. The infusion line may be flushed with normal saline.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison Control Center
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ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

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

Pharmacodynamics

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Pharmacokinetics

Human normal immunoglobulin is immediately bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid; after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Pharmacokinetic parameters for GAMMAGARD LIQUID were determined in Clinical Study 160001 in 22 subjects with hypo- and agammaglobulinemia. In this study, doses of 300 to 450 mg/kg body weight were administered every 21 days for about 6 months. GAMMAGARD LIQUID has a half-life of about 30 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

Pharmacokinetic parameters determined for total IgG are shown below.

Parameter	N	Median	95% CI
AUC _{0-21d} (g·h/dL)	22	545	(490; 603)
C _{max} (mg/dL)	22	1630	(1470; 1750)
C _{min} (mg/dL)	22	848	(772; 1000)
T _{max} (hours)	22	0.25	(0.25; 0.25)
Terminal half-life (days)	22	30.1	(27.1; 43.3)
Incremental recovery (mg/dL)/(mg/kg)	22	1.85	(1.71, 2.14)
In-vivo recovery (%)	22	89	(84; 101)

Similar results (half-life of about 35 days) were obtained in the Clinical Study 160101. More pharmacokinetic data for the product are summarized in Part II of the Product Monograph, Section “Detailed Pharmacology”. The values obtained are comparable to parameters reported for other human immunoglobulins.

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.

Absorption:

Median area under the curve (AUC_{0-21d}) observed in the clinical study 160001 was 545 g·h/dL and maximal concentration in the blood occurs shortly after the intravenous infusion.

Distribution and Metabolism:

After equilibration between intravascular and extravascular body compartments, plasma proteins are eliminated from the plasma at a constant rate, as usually illustrated by a hypothetical two-compartment model¹⁹. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Excretion:

Median half-lives determined in clinical studies 160001 and 160101 were about 30 and 35 days, respectively.

Special Populations and Conditions

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

STORAGE AND STABILITY

Refrigeration storage: Store in a refrigerator (2°C – 8°C) for up to **36 months**. Do not freeze.

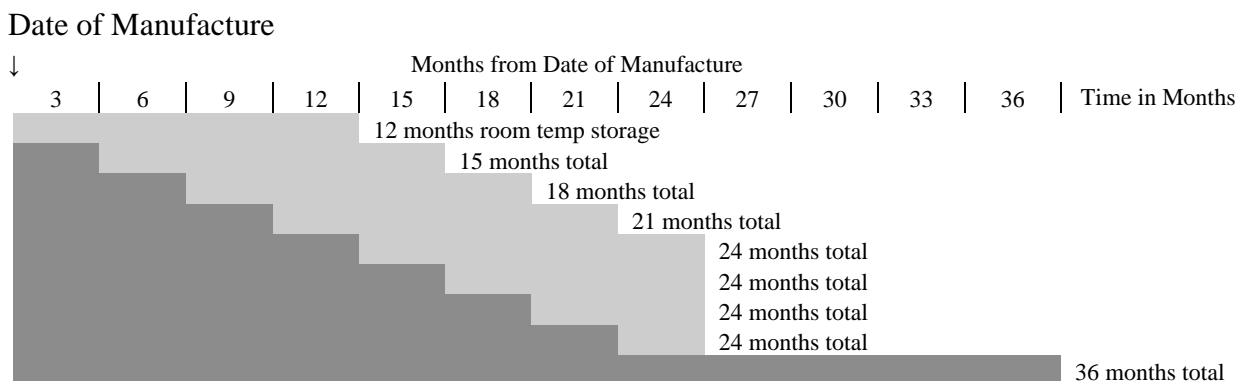
Do not use after the expiry date stated on the label and carton. Keep the vial in the outer carton in order to protect from light.

Room temperature storage: Within the first 24 months from the date of manufacture, GAMMAGARD LIQUID may be stored for a single period of up to 12 months at room temperature (below 25° C). After this period, unused product must be discarded. See below the detailed storage information.

The total storage time of GAMMAGARD LIQUID depends on the point of the time the vial is transferred to room temperature. Examples for storage times are illustrated in Figure 1. If GAMMAGARD LIQUID is stored at room temperature (below 25° C), the date on which carton is removed from refrigerated storage and the new expiry date must be recorded in the area provided on the carton.

The new expiry date will be the shorter of: 24 months from the date of manufacture (indicated on the carton); or 12 months from the date removed from refrigeration. Once removed from refrigeration and stored at room temperature GAMMAGARD LIQUID must be used or discarded and may not be returned to refrigerated storage.”

Figure 1
Storage Guidelines for GAMMAGARD LIQUID



25°C (Room temperature)

2° to 8°C

Example: If the product is taken out of the refrigerator after 3 months, it can be stored for 12 months at room temperature, and the total storage time is 15 months.

SPECIAL HANDLING INSTRUCTIONS

The product should be brought to room or body temperature before use.

Do not use normal saline as a diluent. If dilution to lower concentrations is warranted, 5% dextrose is recommended.

The solution should be clear or slightly opalescent and colourless or pale yellow. Do not use solutions that are cloudy or discoloured or have deposits or particulate matter.

GAMMAGARD LIQUID should only be administered intravenously. Other routes of administration have not been evaluated.

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Solution for infusion administered intravenously.

The composition GAMMAGARD LIQUID is presented in Table I-5 below.

Name of Component	Table I-5 Target Composition of IGIV, 10%						Function
	Unit and/or Percentage Formula						
Protein (with at least 98% IgG)	1 g/vial	2.5 g/vial	5 g/vial	10 g/vial	20 g/vial	30 g/vial	Active ingredient
Other Ingredients							
Glycine	0.25M	0.25M	0.25M	0.25M	0.25M	0.25M	Stabilizing agent
Water for injection	10 mL	25 mL	50 mL	100 mL	200 mL	300 mL	Drug carrier

GAMMAGARD LIQUID is available in 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 pack sizes.

The product is filled into containers of type I glass, which are closed with bromobutyl rubber stoppers.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name and Chemical Name:

Due to the continuous manufacturing process of GAMMAGARD LIQUID before the final formulation steps, no distinct intermediate Drug Substance stage can be defined. The nomenclature provided below therefore refers to the Drug Product, a human normal immunoglobulin for intravenous administration. (IGIV).

- Recommended International Nonproprietary Name (INN): Human Normal Immunoglobulin (IVIg)
- European Pharmacopoeia name: Human Normal Immunoglobulin for Intravenous Administration
- ATC-code: J06BA02
- Chemical name: not applicable
- US Code of Federal Regulations Name (21 CFR J 640.100): Immune Globulin (Human)
- Chemical Abstracts Service (CAS) registry number: not applicable

Molecular formula, molecular mass and Structural Formula:

The active ingredient of GAMMAGARD LIQUID is human polyvalent immunoglobulin G (IgG). Immunoglobulins are made up of four polypeptide chains, comprising two identical light chains of a molecular weight of approximately 25 kD and two identical heavy chains of a molecular weight of approximately 50 kD. The four chains form a three-dimensional Y-shaped structure as shown by X-ray crystallography. Carbohydrate groups are attached covalently at distinct positions of the heavy chains. The overall molecular mass of IgG molecules approximates 150 kD.

Each of the four chains has a variable region at the amino-terminus, which contributes to the antigen-binding site, and a constant region. The constant region of the heavy chains determines the isotype (heavy chain class) of the antibody. Variable and constant regions are divided into a series of homologous domains with similar amino acid sequences that each fold into a distinct globular structure.

The light chains are bonded to the heavy chains by non-covalent associations and by disulfide bonds. Variable regions of light and heavy chains pair to generate two identical antigen-binding sites, which lie at the N-termini of the arms of the Y (in the Fab region) and confer specificity to the antibody. The trunk of the Y, or Fc fragment (fragment crystallizable), is composed of the two carboxy-terminal domains of the two heavy chains. Flexible hinge regions join the Fab and Fc parts of the immunoglobulin. The Fc fragment and hinge regions differ in antibodies of different isotypes, thus determining their functional properties.

Immunoglobulin G is the most common immunoglobulin class, with a level of 9-12 g per liter of plasma, accounting for about 75 % of the total immunoglobulins in plasma of healthy individuals. Immunoglobulin G is further divided into subclasses with different heavy chain isotypes: IgG₁, IgG₂, IgG₃ and IgG₄.

In the GAMMAGARD LIQUID manufacturing process, the native structure of IgG antibodies, as well as the broad antibody diversity and the IgG subclass distribution are maintained during the enrichment of IgG from human plasma.

Physicochemical properties

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

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

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

GAMMAGARD LIQUID is a purified IgG preparation that is isolated from human plasma pools using a modified Cohn-Oncley cold alcohol fractionation process and further purified through chromatographic steps using weak cation (CM Sepharose Fast Flow) and weak anion exchange (ANX Sepharose 4 Fast Flow, low substitution) media. The native structure and function of the IgG molecules are not compromised throughout the process. The IgG is isolated without chemical or enzymatic modification, and the Fc and Fab portion are maintained intact and the

IgG does not activate complement or pre-Kallikrein activity in an unspecific manner. Therefore, the product retains the broad spectrum of antibody specificities and subclass distribution, and the product exerts all the critical biological activities of polyvalent antibody molecules present in human plasma. The distribution of IgG subclasses present in this product is comparable to that found in normal serum (French, 1986).

The immunoglobulins in GAMMAGARD LIQUID are immediately and completely bioavailable in the recipient's circulation after intravenous administration. They are distributed relatively rapidly between plasma and extravascular compartments, ensuring immediate functional activity in the circulation. The half-life of IgG in the circulation is about 3 to 4 weeks. This half-life may vary from patient to patient, in particular in primary immunodeficiency. Immunoglobulins G and IgG complexes are broken down in the cells of the reticuloendothelial system.

Product Characteristics

GAMMAGARD LIQUID is a purified immunoglobulin G (IgG) solution for intravenous infusion. The preparation contains approximately 100 mg of human protein per mL, of which at least 98% is gamma globulin, and has a pH of 4.6 to 5.1. Glycine is used as stabilizing agent and is present at an amount of 0.25M to maintain the product isotonic.

GAMMAGARD LIQUID is available in 6 pack sizes, i.e. 1 g in 10 mL, 2.5 g in 25 mL, 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL and 30 g in 300 mL solution. The product is filled into containers of type I glass, which are closed with bromobutyl rubber stoppers.

The GAMMAGARD LIQUID manufacturing process employs a modified Cohn-Oncley cold alcohol fractionation procedure to isolate an intermediate IgG fraction, referred to as Precipitate G, from frozen human plasma pools. Prior to cold ethanol fractionation 7 different adsorption options for crude coagulation factors and antithrombin III can be performed. Precipitate G is further purified by a continuous process through the use of weak cation exchange chromatography and weak anion exchange chromatography to final formulation. Three dedicated virus reduction steps are included in the downstream purification of Precipitate G, which are solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH and elevated temperature in the final formulation.

GAMMAGARD LIQUID belongs to the pharmacotherapeutic group of immune sera and immunoglobulins, immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02. The active ingredient of GAMMAGARD LIQUID is human polyvalent IgG. The native structure and function of the IgG molecules are not compromised throughout the manufacturing process. Therefore, the product retains the subclass distribution and the broad spectrum of antibody specificities present in human plasma, and exerts all the critical biological

activities of polyvalent antibody molecules. The exact mechanism of action other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

Intravenous immunoglobulins are indicated in primary immunodeficiency syndromes, and in secondary antibody deficiency conditions such as Chronic Lymphocytic leukaemia, multiple myeloma, or allogeneic bone marrow transplantation. They are also recommended for immunomodulation in idiopathic thrombocytopenic purpura (ITP).

Viral Inactivation

The starting material used for the manufacture of GAMMAGARD LIQUID is plasma. The GAMMAGARD LIQUID product can be manufactured from either Source or Recovered Plasma obtained in the United States (US). Plasma is the Human Plasma intended for the manufacture of blood derivatives.

Source Plasma as defined in 21 CFR Part 640, is the fluid portion of human blood collected by manual or automated plasmapheresis and intended as source material for further manufacturing. Source plasma is frozen to -20° C or below within 30 minutes of donation.

Recovered Plasma is defined as human plasma obtained from a single unit of whole blood and intended for further manufacturing use. Recovered plasma is separated from whole blood and frozen within 24 hours of donation. Recovered plasma complies with the standards described in *21 CFR Part 640.34 (a), Recovered Plasma*.

Recovered plasma classified as 24 hour plus Recovered Plasma (24H+) may also be used in the manufacture of GAMMAGARD LIQUID and falls under the following two categories:

- Recovered Plasma Category 19804 - prepared from fresh frozen Recovered plasma by rapid freeze-thawing process followed by the removal of cryoprecipitate through centrifugation. The cryo-depleted plasma unit is re-frozen for storage at -20°C or colder. This is referred to as 24 H + Cryo-depleted Recovered plasma.
- Recovered Plasma Category 19861 - prepared from whole blood that has been stored from 24 to 72 hours prior to centrifugation for recovery of plasma followed by freezing (at -20°C or colder). This is referred to as 24 H + Cryo-rich Recovered Plasma.

Plasma Screening

Screening for Source Plasma

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

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

- HIV- 1/2 antibody non- reactive
- HBsAg non-reactive
- HCV antibody non-reactive
- HIV-1 NAT^b non-reactive
- HCV NAT^b non-reactive

Although not required by the FDA and Health Canada, Takeda also performs Hepatitis B Virus (HBV), Hepatitis A Virus (HAV) and ParvoVirus B-19 (PVB19) testing by NAT, in mini-pool format, on single plasma donations.

The criteria for release are as follows:

- HBV^c non-reactive
- HAV non-reactive
- PVB19 <1.8 x 10³ IU PVB19 DNA/ML

Tests carried out on the Manufacturing Plasma Pools

Each manufacturing plasma pool prepared for the manufacture of plasma derivatives is also tested for HBsAg and HIV-1/2 antibodies, as well as by NAT. Only plasma pools negative by NAT for HIV, HBV, HCV, HAV and not exceeding 10⁴ IU PVB19 DNA/ml are released for further manufacture.

System to Trace the Path of Any Donation

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

^b Tested in mini-pool format

^cFor Recovered Plasma, NAT testing is performed on anti-HBc repeat reactive samples

Three dedicated virus clearance steps, each working by different mechanisms, have been integrated into the GAMMAGARD LIQUID manufacturing process:

- Solvent/Detergent (S/D) treatment of redissolved Precipitate G (an effective inactivation step for lipid-enveloped viruses)
- 35 nm Nanofiltration (an effective virus removal step of lipid-enveloped and non-lipid-enveloped viruses)
- Incubation at low pH and elevated temperature of the final filled product (an effective inactivation step of lipid-enveloped viruses and some non-lipid-enveloped viruses; contributes to viral safety with respect to Parvoviruses)

For these three dedicated virus clearance steps, comprehensive virus clearance studies have been performed, including all the required hold controls, cytotoxicity and interference assays necessary to allow full interpretation of the data. In each study, the validity of the scaled-down process has been confirmed by measuring process and biochemical parameters and comparing these with data from the large-scale manufacturing process. The robustness of virus clearance has also been investigated by adjusting critical process parameters to levels least favorable for virus inactivation (e.g. temperature, incubation time, concentration of S/D components, etc.) and by varying other parameters in different runs.

The potential impact of different adsorption options^d at manufacturing scale at the cryosupernatant level (i.e. far upstream of the dedicated virus clearance steps) has also been investigated by using test articles produced by adsorption options 1, 3 and 6, representing the extremes (Option 1 and 6) of the number of adsorption steps used^e.

CLINICAL TRIALS

Study demographics and trial design

Studies **160001** and **160101** included subjects diagnosed with PID. In study **160002** subjects diagnosed with ITP were included. All treated subjects were included in the safety analyses for each of the respective studies (**160001**: n=22; **160101**: n=61 and **160002**; n=23). The inclusion criteria of study **160101** required subjects to be > 24 months of age, and the youngest subject included in the per-protocol population was 6 years old. In studies **160001** and **160002**, subjects

^d At the cryosupernatant level, several coagulation factors/inhibitors, which are present at this stage in trace amounts, may be removed by adsorption onto DEAE-Sephadex or aluminum hydroxide at manufacturing scale.

^e Selecting adsorption Options 1, 3 and 6 brackets the available adsorption Options 1-7: Option 1 provides for the minimal number of adsorptions, i.e. none; Option 3 provides for an intermediate number of adsorptions, i.e. two; and Option 6 provides for the maximum number of adsorptions, i.e. three, performed at the cryosupernatant stage of the manufacturing process.

had to be at least 18 years old in order to be included. The median age of subjects in studies **160001**, **160101** and **160002** was 47, 34 and 49 years, respectively. The majority of subjects in all three studies were Caucasian, only two subjects were Black, and 1 was Asian (all three in the per-protocol population in study **160101**).

Study **160604** included 44 subjects diagnosed with Multifocal Motor Neuropathy (MMN). The inclusion criteria of study 160604 required subjects to be at least 18 years of age, the 44 subjects enrolled, ranged in age from 31 to 72 years old with a median of 52 years. A greater number of male than female subjects participated in the study (72.7% versus 27.3%), which reflects the known gender distribution of MMN.³⁷ A total of 41 subjects completed the study.

Study Design

Study **160001** was a prospective, open-label, uncontrolled, multi-center study designed to investigate the pharmacokinetics, efficacy, and safety of GAMMAGARD LIQUID Solution in subjects (≥ 18 years of age) with PID (hypo- or agammaglobulinemia) (N=22). Subjects were treated every 21 days, initially (first 3 infusions) with GAMMAGARD S/D (reconstituted to a 10% solution), which was administered to standardize the IgG replacement therapy of all subjects to the same i.v. product and to acquire data with a licensed product. This was followed by treatment with GAMMAGARD LIQUID for the remaining 9 infusions.

Pharmacokinetic parameters for the primary endpoint included in-vivo recovery, half life, and trough levels of total immunoglobulin G (IgG) after treatment with GAMMAGARD LIQUID.

Efficacy endpoints were rate of infections and frequency of antibiotic use. The safety endpoints for this study were the number of treatment-related AEs, changes in vital signs and laboratory parameters.

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Median age (range)	Gender
160001	Open-label, uncontrolled, multi-center study	300-450 mg/kg BW. every 3 weeks; I.V.; 3 infusions with Gammagard S/D, 9 infusions with GAMMAGARD LIQUID	22 adult subjects with PID were treated	Median age: 47 years; Range 26-70 years	Females: N=8; Males: N=14

Study **160101** is a randomized, double-blinded, uncontrolled, multicenter trial designed to evaluate the safety and efficacy of GAMMAGARD LIQUID in subjects (> 24 months of age) with PID (N=61). The study used final product manufactured using 3 upstream manufacturing pathway options (options 1, 3, and 6) to ensure consistency of the pharmacokinetic and safety profiles of final product. The order of administration of product of different manufacturing options was randomized and both the investigator and the subject were blinded with respect to the administration sequence. Subjects were treated at 21 to 28 day intervals for a minimum of 12 months (efficacy period). After Month 12, subjects had the option to continue treatment. Safety data was to be collected for subjects continuing treatment beyond the 12-month efficacy period.

The primary efficacy endpoint of the study was the rate of acute serious bacterial infections per subject per year. Acute serious bacterial infections were documented infections including bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, or the presence of visceral abscesses that met specific diagnostic criteria (i.e. were validated), as defined by the US Food and Drug Administration (FDA). The mean rate of acute serious bacterial infections was to be compared with a hypothesized rate of 1 serious acute bacterial infection/subject/year, in accordance with current guidelines of the FDA Blood Products Advisory Committee (BPAC)¹⁸. Secondary efficacy endpoints were the rates of validated other bacterial infections commonly occurring in subjects with PID and the number of hospitalizations secondary to infectious complications. Pharmacokinetic parameters for GAMMAGARD LIQUID also were determined.

The primary safety endpoint of the study was the percentage of GAMMAGARD LIQUID infusions with 1 or more temporally associated AEs, i.e., AEs occurring during an infusion or within 72 hours of completion of an infusion. This percentage was compared with a hypothesized rate of 40% of infusions with temporally associated AEs, in accordance with current guidelines of the FDA BPAC¹⁸.

Secondary safety endpoints included 1) the percentage of infusions with one or more AEs judged by the investigator to be causally related to the study product; and 2) the percentage of GAMMAGARD LIQUID infusions with both temporally and causally associated AEs. Causally associated AEs were AEs that occurred any time during or after an infusion and were deemed by the investigator to be related to the study product.

Table II-2					
Summary of patient demographics for the US clinical trials in PID (160101)					
Study #	Trial design	Dosage, route of administration and duration	Study subjects	Median age (range)	Gender
160101	Randomized, double-blinded,	300-600 mg/kg BW. every 21-28	61 subjects with PID,	Median age:	Females:

	uncontrolled, multicenter	days; I.V.; one year, with the option to continue treatment	older than 24 months of age were treated	34 years, Range: 6-72 years	N=33 Males: N=28
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Study **160002** was designed as a prospective, open-label, non-controlled, multi-center trial in subjects ≥ 18 and ≤ 65 years of age (N=23) who had been diagnosed with ITP at least 6 months prior to study entry. After screening, subjects received a total dose of 2 g of GAMMAGARD LIQUID per kg body weight equally divided over 2 to 5 days. A maximum of 2 booster doses each ranging from 400 mg to 1,000 mg per kg body weight were permitted if the subject's platelet count dropped to $\leq 20 \times 10^9/L$. Subjects who achieved a platelet increase to $\geq 50 \times 10^9/L$ at least once prior to Day 15 after initiation of treatment and did not require a booster dose before Day 15 after onset of the treatment course were considered treatment responders and were followed until Day 29. Non-responders terminated the study on Day 15. Platelet counts were determined at screening and on Days 1 (initiation of treatment course), 2, 5, 8, 11, 15, 22, and 29. Blood samples for platelet determination taken on treatment days were drawn prior to study drug administration.

The primary efficacy endpoint was the number of subjects who were treatment responders. Secondary efficacy endpoints were the time to platelet response, duration of response, maximum platelet level achieved, and regression of hemorrhage. Safety was assessed by adverse experiences (AEs), and changes in vital signs, clinical chemistry and hematological parameters.

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Median age (range)	Gender
160002	Prospective, open-label, non-controlled, multi-center trial	2 g/kg BW. given on 2-5 days, up to 2 booster doses (0.4-1 g) were allowed; I.V.; 4 weeks	23 adult subjects with chronic ITP were treated	Median age: 49 years; Range: 18-68 years	Females: N=10 Males: N=13

Study **160604**, 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 Multifocal Motor Neuropathy (MMN). The study examined grip strength in the more affected hand (measured with dynamometer), and Guy's Neurological Disability Scale (GNDS) [upper limb part 6 subsection]. 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 (3 stabilization phases, one randomized withdrawal and one cross-over period). If during 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 $\geq 50\%$ 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-two subjects were evaluated to demonstrate effectiveness of GAMMAGARD LIQUID to improve or maintain muscle strength and functional ability in patients with MMN.

Study Results

Table II-4 Results of study number 160001		
Primary Endpoint	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
<i>In-vivo</i> recovery, (terminal) half life, and trough levels of total immunoglobulin G (IgG) after treatment with GAMMAGARD LIQUID	IVR (median): 89%; T _{1/2} (median): 30.1 days; Steady state trough levels (total IgG, median): 851 mg/dL	Subjects were treated initially (3 infusions) with GAMMAGARD S/D to standardize the IgG replacement therapy of all subjects to the same i.v. product Steady state trough levels (total IgG, median): 817 mg/dL

Table II-5 Results of study number 160101		
Primary Endpoint	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Primary efficacy endpoint of the study was the rate of acute serious bacterial infections per subject per year	No acute serious bacterial infections were reported in any of the 61 treated subjects with PID in this study. The observed rate of acute serious bacterial infections was significantly less ($p \ll 0.0001$) than the hypothesized rate (i.e. 1 per year)	Not applicable
Primary safety endpoint of the study was the percentage of GAMMAGARD LIQUID infusions with 1 or more temporally associated AEs, i.e., AEs occurring during an infusion or within 72 hours of completion of an infusion	For all treated subjects (N=61), the percentage of infusions with temporally associated AEs including the first infusion (23.73%) and excluding the first infusion (22.35%) was significantly less ($p \ll 0.0001$) than the hypothesized rate of 40%.	Not applicable

Table II-6 Results of study number 160002		
Primary Endpoint	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Primary efficacy endpoint was the number of subjects who were treatment responders	Of the 21 subjects who fulfilled all selection criteria, 15 (71.4%) were treatment responders. This rate of treatment responders is similar to the rates reported in the literature.	Not applicable

GAMMAGARD LIQUID was shown to be safe and well tolerated in the clinical studies in a total of 106 subjects. Plasma samples have been assessed for viral safety in clinical study 160101 (N=61 subjects). No seroconversions for HBV, HCV, HIV-1, and HIV-2 were observed following treatment with GAMMAGARD LIQUID. Regarding tolerability, a list of drug-related adverse events for each clinical study is included in Part I, section “Clinical Trial Adverse Drug Reactions”.

Multifocal Motor Neuropathy (MMN)

Primary Safety Endpoints

- The rate of temporally associated AEs per infusion defined as the total number of all AEs that began during infusion or within 72 hours of completion of an infusion, irrespective of being related or not related to the study product, divided by the total number of infusions
- The proportion of subjects for whom the infusion rate of any infusion was reduced and/or the infusion was interrupted or stopped for any reason
- The proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped for any reason
- The proportion of subjects reporting one or more moderate or severe AEs that began during infusion or within 72 hours of completion of an infusion

Secondary Safety Endpoints

- The rate of serious adverse events (SAEs) per infusion defined as the total number of SAEs determined by the investigator to be related to the study product that occur at any time during the study (“related”) divided by the total number of infusions
- The proportion of subjects for whom the infusion rate of any infusion was reduced and/or the infusion was interrupted or stopped for tolerability concerns/AEs
- The proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped for tolerability concerns/AEs

- The rate of AEs per infusion defined as the total number of AEs determined by the investigator to be related to the study product that occur at any time during the study (“related”) divided by the total number of infusions
- The number of all AEs/related AEs categorized by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, seriousness, relatedness to the study product and severity
- The rate of AEs/related AEs defined as the number of AEs/related AEs categorized by MedDRA preferred terms, seriousness, relatedness to the study product and severity, divided by the number of infusions
- The proportion of infusions associated with one or more AEs related to the study product

Primary Efficacy Endpoints

- Grip strength in the more affected hand, measured using a DynEx digital dynamometer.
- Upper limb (Part 6) subsection of the Guy’s Neurological Disability Scale (GNDS).

Secondary Efficacy Endpoints

- Percentage of subjects with at least a 30% decline in grip strength in the more affected hand (measured using a DynEx digital dynamometer)
- Number and percentage of subjects with a decline in grip strength in the less affected hand (measured using a DynEx digital dynamometer)
- Number of subjects with accelerated switch (from the placebo vs. the IGIV, 10% blinded treatment) to the next stabilization phase during the Cross-Over Periods 1 and 2
- Patient assessment of disability assessed according to the Patient Global Impression of Change scale
- Overall Disability Sum Score
- Timed Peg Board Test
- Patient assessment on visual analog scale (VAS): Endpoints of the 10 cm scale: No symptoms – disabled, unable to use affected limbs

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 II-7). 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 II-7
Relative Change in Grip Strength in the More Affected Hand during Cross-over Period (ANOVA)
(Intent-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) 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 II-8). 4.8% of subjects showed deterioration with both placebo and GAMMAGARD LIQUID, while 47.6% showed no deterioration on either.

Table II-8
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 $\geq 30\%$ 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 $\geq 30\%$

decline during treatment with GAMMAGARD LIQUID, but not during placebo. A relative decline of $\geq 30\%$ 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 $\geq 30\%$ 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 no change in disability) during treatment with GAMMAGARD LIQUID.

At the end of the placebo period, subjects required 17% longer to complete the 9-hole peg test (a measure of dexterity) with the dominant hand, and 33% longer with the nondominant hand, compared to baseline. During GAMMAGARD LIQUID treatment, dexterity increased by a mean of 1.2% compared to baseline in the dominant hand and 6.7% in the non-dominant hand.

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.

Comparative Bioavailability Studies

No classical biopharmaceutic studies (e.g. bioavailability, comparative bioavailability, or bioequivalence) have been performed with GAMMAGARD LIQUID. However, to ensure consistency among the spectrum of adsorption pathway options, pharmacokinetic and safety data were analyzed for final product manufactured from 3 adsorption pathway options (representing the 7 pathway options foreseen in the manufacturing of GAMMAGARD LIQUID).

DETAILED PHARMACOLOGY

Clinical Study 160001

The primary pharmacokinetic endpoints of study 160001 were the in-vivo recovery, half-life and trough levels of total IgG of GAMMAGARD LIQUID. Other pharmacokinetic parameters assessed for GAMMAGARD LIQUID were area under the curve (AUC), maximum concentration (C_{max}), minimum concentration (C_{min}), time to maximum concentration (T_{max}), and incremental recovery. Pharmacokinetic parameters were also determined for IgG subclasses (IgG₁, IgG₂, IgG₃, IgG₄). Trough levels of total IgG for GAMMAGARD S/D were also determined.

For determination of pharmacokinetic parameters, testing for total serum IgG and IgG subclasses was performed on serum samples collected directly before and 15 minutes (\pm 5 minutes) after completion of infusion of GAMMAGARD LIQUID, and on Days 1, 3, 7, 14 (\pm 2 days) and 21 (\pm 2 days, i.e., directly before the next infusion).

Pharmacokinetic parameters determined for total IgG are shown in Part I, section “Pharmacokinetics”, Table I-6.

The median terminal half-life of 30.1 days is consistent with data reported for Takeda’s licensed IGIV products^{20,21}. The in-vivo recovery was slightly lower than expected. All other parameters are consistent with data reported in the literature^{22,23,24,25,26 27,28,29,30, 31,32,33}.

Pharmacokinetic parameters were also determined for IgG subclasses (IgG₁, IgG₂, IgG₃, IgG₄). The median terminal half-lives of 28.3, 31.3, 20.9 and 24.2 days for subclasses IgG₁, IgG₂, IgG₃ and IgG₄, respectively, are in accordance with data reported in the literature.

Trough levels of total IgG were determined prior to each IGIV infusion. Total IgG steady state trough levels for GAMMAGARD LIQUID per subject were estimated as the geometric mean of the subject’s last 2 measurements (i.e., the 8th and 9th infusion of GAMMAGARD LIQUID). Total IgG steady state trough levels for GAMMAGARD LIQUID were summarized over the set of subjects by medians and non-parametric 95% CIs for the medians.

The dose of study drug administered was sufficient to maintain a median steady state trough level of total IgG of 817 mg/dL (95% CI: 756; 905) after administration of GAMMAGARD S/D, and of 851 mg/dL (95% CI: 756; 1006) after administration of GAMMAGARD LIQUID.

Clinical Study 160101

The pharmacokinetic parameters of GAMMAGARD LIQUID were evaluated after 4 consecutive infusions of study product. Blood was drawn for evaluation of serum total IgG levels at pre-infusion, 30 minutes, and 1, 4, 10, 14, and 21 to 28 days after the infusion.

Pharmacokinetic parameters for GAMMAGARD LIQUID are summarized below in Table II-9.

Parameter	N	Median	95% CI
AUC _{0-21d} (mg·days/dL)	57	29139	(27494, 30490)
C _{max} (mg/dL)	57	2050	(1980, 2200)
C _{min} (mg/dL)	57	1030	(939, 1110)
Terminal half-life (days)	57	35	(31, 42)
Incremental recovery (mg/dL)/(mg/kg)	57	2.3	(2.2, 2.6)
In-vivo recovery (%)	57	112	(104, 121)

Abbreviations: N = number of subjects; 95% CI = 95% confidence interval.

Four subjects were excluded from the pharmacokinetic dataset: 3 subjects did not have IgG measurements for all the required timepoints and 1 subject did not complete Infusion 4.

The ability of the dosing regimen to maintain acceptable IgG levels between infusions was assessed by determining total IgG trough levels prior to each infusion. Median total IgG trough levels were maintained between 960 and 1215 mg/dL throughout the duration of the efficacy period of the study.

The data demonstrate that the pharmacokinetic characteristics of GAMMAGARD LIQUID are consistent with those reported in the literature. The half-life is consistent with that reported for Takeda's licensed IGIV products^{20, 21} as well as those reported for other IGIV products^{34, 35, 36}. The dosing regimen was sufficient to maintain IgG trough levels above the threshold level prescribed by the protocol (> 450 mg/dL).

In clinical study 160101, the pharmacokinetics and safety of GAMMAGARD LIQUID were evaluated descriptively according to the adsorption pathway (i.e. options 1, 3, and 6) used to produce study product. Overall mean trough levels for the entire efficacy period were consistent for study product produced by each of the 3 pathways, and all were above the protocol-specified threshold of 450 mg/dL. The percentages and 95% CIs of infusions with temporally or causally, or both causally and temporally associated AEs indicated that final product manufactured using each of the 3 pathway options had a consistent safety profile.

Clinical Study 160604

In contrast to patients who require replacement therapy with IGIV, which aims to restore deficient serum immunoglobulins to within the physiological range, individuals with MMN generally have normal levels of endogenous immunoglobulins³⁷, and there is no known association between IgG trough levels and clinical response. As expected, in Study 160604, high median trough levels of total IgG were determined across all study parts in which IGIV, 10% was administered (median 16.40 g/L; 95% CI: 15.70; 17.10)

Comparison and Analyses of Results Across Studies

Pharmacokinetic parameters for total IgG were summarized over the US and European studies of GAMMAGARD LIQUID in subjects with PID (Clinical studies 160101 and 160001).

Table II-10 below shows the median and 95% confidence interval for C_{max} , C_{min} , in-vivo recovery, incremental recovery, AUC, and half-life for the pooled data of the 2 studies.

Parameter	Unit	Study	N	Median	95% CI for median
C_{max}	(mg/dL)/(mg/kg)	Pooled 160001 and 160101	79	4.47	4.08 to 4.78
C_{min}	(mg/dL)/(mg/kg)	Pooled 160001 and 160101	79	2.25	2.11 to 2.43
In-vivo recovery	%	Pooled 160001 and 160101	79	104	98 to 114
Incremental recovery	(mg/dL)/(mg/kg)	Pooled 160001 and 160101	79	2.17	2.05 to 2.36
AUC 0-21/28	(g/dL.h)/(mg/kg)	Pooled 160001 and 160101	79	1.60	1.51 to 1.77
Half-life	days	Pooled 160001 and 160101	79	32.5	30.8 to 37.6

FADS: Full Analysis Data Set

While for entry in clinical study 160101 subjects had to be > 24 months of age, only adult subjects >18 years were enrolled in clinical study 160001. Therefore, pharmacokinetic parameters were analyzed separately for children (12 years or below, N=5), adolescents (13 to 17 years, N=10) and adults (18 or above, N=64).

The individual pharmacokinetic parameters with the exception of half-life are consistent in the 3 age groups. The median half-life is 41.3 days (93.75% CI 20.2 to 86.8) for children (N = 5) and 45.1 days (95% CI 27.3 to 89.3) for adolescents (N = 10), while the pooled data for adults (N = 64) show a median half-life of 31.6 days (95% CI 29.0 to 36.1). The values in children and adolescents are inconclusive because of the small number of subjects in these 2 groups and the large variance which resulted in the wide CIs. AUC and trough levels were similar in children, adolescents and adults.

MICROBIOLOGY

Not Applicable

TOXICOLOGY

Four GLP-compliant studies are summarized below.

Three lots of GAMMAGARD LIQUID were studied in each of the following three experiments. Acute toxicity was tested in mice and rats, two lots of Gammagard S/D served as references. Local tolerance was investigated in the rabbit ear, one lot each of Gammagard S/D and Gamimmune N, 10 % was used as a standard.

An Ames test in *Salmonella typhimurium* strains was run for one lot of IGIV, 10 % TVR Solution to test for mutagenicity.

Literature data on pharmacokinetics and toxicity of the solvent/detergent reagents are presented.

Single-Dose Toxicity

Determination of Acute Toxicity in Mice after Intravenous Administration of GAMMAGARD LIQUID

The acute toxicity of GAMMAGARD LIQUID (lot nos. 01C21AN11, 01C21AN21, and 01D05AN11) was compared with Gammagard S/D (active control; lot nos. 99H25AB11 and 00G07AX11) in doses of 2,500, 5,000, and 10,000 mg/kg (25, 50, and 100 mL/kg). Formulation buffer for GAMMAGARD LIQUID (25, 50, and 100 mL/kg) and isotonic saline (100 mL/kg) served as negative controls. The test and reference items were injected intravenously into animals divided into 19 groups of 10 mice (5 male, 5 female) each.

The mice were observed for 14 days for clinical symptoms including unusual behavior. The animals were weighed at days 0, 7, and 14 to provide an indication of general health and the number of deaths was recorded. At the end of the observation period the surviving animals were humanely exterminated by CO₂ inhalation and examined pathologically.

Mortality is described in Table II-11 below

Table II-11 Mortality in mice			
Study arm	Dose/Volume (mg or mL/kg)	Mortality	
		x/n	%
IGIV, 10 % TVR Solution	2500	0/30	0
	5000	0/30	0
	10000	2/30	6.7
Gammagard S/D	2500	0/20	0
	5000	8/20	40
	10000	20/20	100
Formulation Buffer	25	0/10	0
	50	0/10	0
	100	0/10	0
Isotonic Saline	100	0/10	0

Transient clinical symptoms (behavioral depression, dyspnea) indicative of acute toxicity were observed in the surviving animals which had received the intermediate dose of Gammagard S/D (6/12; 50 %) or the highest dose of GAMMAGARD LIQUID (16/28; 57 %).

Growth rate in animals treated with GAMMAGARD LIQUID or Gammagard S/D was nearly the same or slightly higher than in those treated with isotonic saline.

Pathological findings (indicative of volume overload) were found only in the animals that died during or after injection of test or active reference items.

The "No Observed Adverse Effect Level" for GAMMAGARD LIQUID for this study in mice was 5,000 mg/kg, but 2,500 mg/kg for Gammagard S/D.

Determination of Acute Toxicity in Rats after Intravenous Administration of Immunoglobulin Intravenous (Human), 10 % Triple Virally Reduced Solution

The acute toxicity of IGIV, 10 % TVR (lot nos. 01C21AN11, 01C21AN21, and 01D05AN11) was tested in rats, compared with Gammagard S/D (active control; lot nos. 99H25AB11 and 00G07AX11), formulation buffer and isotonic saline (negative controls). The test and reference items were injected intravenously into animals divided into seven groups of ten rats (five males, five females) each. All animals received a volume of 20 mL/kg, the maximum volume feasible as a bolus injection in rats (limit test; immunoglobulin dose = 2,000 mg/kg).

The rats were observed for 14 days for clinical symptoms including unusual behavior. The animals were weighed on days 0, 7 and 14 to provide an indication of general health. At the end of the period of observation the animals were sacrificed by CO₂ inhalation and examined pathologically.

All animals survived for the test period. Clinical symptoms indicative of acute toxicity (behavioral depression, dyspnea) were observed in the Gammagard S/D groups only. Compared with isotonic saline, no statistically significant influence of the active treatment (IGIV, 10 % TVR) or the active control (Gammagard S/D) could be detected on the growth rate during the first 2 weeks after injection. No treatment-related findings were revealed by gross necropsy.

The "No Observed Adverse Effect Level" for IGIV, 10 % TVR was 2,000 mg/kg but below 2,000 mg/kg for Gammagard S/D.

Repeat-Dose Toxicity

Repeat dose toxicity was not investigated since a human protein in any xenogenic animal model would either be metabolized more quickly or even would cause severe antigenic reactions that are not representative for humans.

Genotoxicity

Salmonella typhimurium Reverse Mutation Test

An Ames test was performed for one lot of IGIV, 10 % TVR (no. 01C21AN11). Five concentrations ranging from 1.2 to 100 µL per plate were tested either with or without external metabolization (external metabolising system: S9-mix from Aroclor 1254 – induced rat livers). The bacterial strains *Salmonella typhimurium* TA97a, TA98, TA100, TA102, and TA1535 were used as test system.

The test substance at a concentration of 100 µL per plate had no toxic effects on the strains. No statistically significant increase of the mutation frequency was detected for any of the tested concentrations or any bacterial strain in the absence of external metabolization compared with the negative control samples. Metabolic activation did not change these results.

Carcinogenicity

No studies were conducted regarding carcinogenicity since the metabolization of polyclonal human GAMMAGARD LIQUID does not lead to any degradation of the product that could cause carcinogenicity. According to *Note for Guidance on Preclinical Safety Evaluation of Biotechnology – Derived Pharmaceuticals (CPMP/ICH/302/95)*, which also addresses plasma-derived products, carcinogenicity studies "are generally inappropriate."

Reproductive and Developmental Toxicity

No studies were conducted regarding Reproductive and Developmental Toxicity since the metabolization of polyclonal human GAMMAGARD LIQUID does not lead to any degradation of the product that could cause reproduction or developmental toxicity. According to *Note for Guidance on Preclinical Safety Evaluation of Biotechnology – Derived Pharmaceuticals (CPMP/ICH/302/95)*, which also addresses plasma-derived products, genotoxicity studies "are not needed."

Local Tolerance

Investigation on Local Tolerance of Immunoglobulin Intravenous (Human), 10 % Triple Virally Reduced Solution in Rabbits

The local tolerance of IGIV, 10 % TVR was tested after intra-arterial, intravenous and paravenous application in rabbits. Three lots of IGIV, 10 % TVR (nos. 01C21AN11, 01C21AN21, and 01D05AN11) were compared with one lot each of Gammagard S/D (no. 99H25AB11) and Gamimune N, 10 %, an immunoglobulin preparation with low pH (no. 648W007A) (both active controls) or formulation buffer (negative control). Each of the six items was either infused intra-arterially (10 min), or intravenously (60 min) both at a volume of 10 mL, or injected paravenously at a volume of 0.5 mL into the right ear of each of 4 rabbits (2m, 2f), resulting in a total of 72 rabbits. An equivalent volume of isotonic saline was given as a negative control to the left ear by the same route.

The behavior of the animals was observed and the injection sites were examined macroscopically for changes for the first 30 min after treatment, thereafter intermittently up to 6 h and again at 24 h, 48 h, and 72 h.

For histopathological examination, tissue sections were collected from: a site distal to the injection site and one at the tip of the ear supplied by the artery after intra-arterial application, a site proximal to the injection site after intravenous application, and the injection site after paravenous application. After sectioning and staining the sections were examined microscopically. Histopathological evaluation focused on damage to the endothelium for intra-arterial and intravenous administration. Perivascular inflammation of connective tissue was evaluated for all three routes of administration. For intra-arterial infusion the artery itself and the supply area (tip of the ear) were examined. Each observation was quantified according to a scoring system from 0 (no alteration) to 3 (severe alteration).

No alterations in behavior were seen in the animals during the observation period. Examined macroscopically, the intra-arterial and paravenous treatment groups showed slight irritation with all the test and active control items. Groups receiving intravenous infusions were normal and no

irritations were visible with formulation buffer and saline. The histological results generally reflected those observed macroscopically (Table II-12).

Table II-12				
IGIV, 10 % TVR, local tolerance, histological scores				
Item	Lot Nos.	Mean histological score		
		intravenous¹	intra-arterial²	paravenous¹
IGIV, 10 % TVR Solution	01C21AN11	0	0.1	0.5
	01C21AN21	0	0.3	0.9
	01D05AN11	0	0.2	0.5
Gammagard S/D	00H25AB11	0	0.3	0.6
Gamimune N, 10 %	648W007A	0	0.1	0.9
Formulation Buffer	01D26AT11	0	0	0.1

¹ 4 observations (= 4 animals)

² 8 observations (= 4 animals; artery and tip of the ear)

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PART III: PATIENT MEDICATION INFORMATION

GAMMAGARD LIQUID®

Immunoglobulin Intravenous (Human), [IGIV] 10%

This leaflet is part III of a three-part “Product Monograph” published when GAMMAGARD LIQUID was approved for sale in Canada and is designed specifically for Patients. This leaflet is a summary and will not tell you everything about GAMMAGARD LIQUID. Contact your Healthcare professional about your medical condition and treatment and ask if there is any new information about GAMMAGARD LIQUID or if you have any questions about the drug.

ABOUT THIS MEDICATION

What is GAMMAGARD LIQUID used for?:

GAMMAGARD LIQUID is used for the following:

- **Primary immunodeficiency**

Replacement therapy in primary immunodeficiency syndromes (PID) such as:

- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Wiskott Aldrich syndrome

- **Secondary Immunodeficiency**

Replacement therapy in secondary immunodeficiency syndromes (SID) such as:

- B-cell chronic lymphocytic leukemia
- Pediatric HIV infection
- Allogeneic bone marrow transplantation

- **Idiopathic thrombocytopenic purpura (ITP)**

- **Multifocal Motor Neuropathy (MMN)**

- Maintenance therapy to improve muscle strength and disability in adult patients with MMN.

How does GAMMAGARD LIQUID work?:

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

Do not use GAMMAGARD LIQUID if:

GAMMAGARD LIQUID must not be used

- If you are hypersensitive (allergic) to immunoglobulins or to the other ingredient of GAMMAGARD LIQUID.
- If you have an immunoglobulin A deficiency (lack of IgA antibodies), you may have antibodies against immunoglobulin A in your blood. Since GAMMAGARD LIQUID contains small amounts of immunoglobulin A (average concentration of 37 mcg/mL), you might develop an allergic reaction.

What are the ingredients in GAMMAGARD LIQUID?:

The active substance is human normal immunoglobulin

GAMMAGARD LIQUID contains 10% (100 mg/mL) of human protein of which at least 98% is immunoglobulin G (IgG). The other ingredients are glycine and water for injections.

GAMMAGARD LIQUID is a 10 % solution (100 mg/mL) for intravenous infusion. The solution is clear or slightly opalescent and colorless or pale yellow.

What the important nonmedicinal ingredients are:

The other ingredients are glycine and water for injections.

GAMMAGARD LIQUID comes in the following dosage forms:

GAMMAGARD LIQUID is available in packages of 1 g in 10 mL, 2.5 g in 25 mL, 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL and 30 g in 300 mL pack sizes.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Immunoglobulin Intravenous (IGIV) products have been reported to cause:

- Disease of the kidneys
- Failure of the kidneys
- Damage to the tubes inside of the kidneys
- Thromboembolic events• Death

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

People with increased risk to blood clots in their veins or arteries include those that have high blood pressure, diabetes mellitus, history of blood vessel disease or previous clots, acquired or inherited increased numbers or activity of platelets which help the blood clot, prolonged periods of not moving, such as lying in bed, increased activity of the proteins that make blood clot, conditions, obesity, advanced age, use of estrogens, long term catheters that go into a central vein, and other cardiovascular risk factors. Thrombosis may occur even in the absence of known risk factors.

GAMMAGARD LIQUID does NOT contain sucrose.

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

INTERACTIONS

- Please inform your healthcare provider if you are taking, or have recently taken any other medicines, even those not prescribed, or if you have received a vaccination during the last six weeks.
- Infusion of immunoglobulins like GAMMAGARD LIQUID may impair the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox vaccines. Therefore, after receiving immunoglobulins you may have to wait up to 3 months before receiving your

live-attenuated vaccine. You may have to wait for up to 1 year after receiving immunoglobulins before you receive your measles vaccine.

- GAMMAGARD LIQUID contains a wide variety of different antibodies, some of which can affect blood tests. If you have a blood test after receiving GAMMAGARD LIQUID, please inform the person taking your blood or your doctor about your infusion.

PROPER USE

Usual dose:

GAMMAGARD LIQUID is intended for intravenous administration (infusion into a vein). It is given to you by your doctor. Dosage will vary depending on your condition and your bodyweight. The following instructions are to help your doctor administer the best dose for you.

Indication	Dose	Frequency of Injections
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 – 0.8 g/kg BW - thereafter: 0.2 – 0.8 g/kg BW	every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L
Replacement therapy in secondary immunodeficiency Allogeneic bone marrow Transplantation Treatment of infections and prophylaxis of graft-versus host disease Persistent lack of antibody production	0.2 – 0.4 g/kg BW 0.5 g/kg 0.5 g/kg	every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L every week from day -7 up to 3 months after transplantation every month until antibody levels return to normal
Idiopathic thrombocytopenic purpura	0.8 – 1 g/kg BW or 0.4 g/kg BW/d	on day 1, possibly repeated once within 3 days for 2 – 5 days
Multifocal Motor Neuropathy (MMN)	0.5 – 2.4 g/kg	every month based on clinical response

BW - bodyweight d -day

At the beginning of your infusion you will receive GAMMAGARD LIQUID at a slow rate (0.5 mL/kg of bodyweight/hour for 30 minutes). Depending on how comfortable you are your doctor may then gradually increase the infusion rate to a maximum of 8 mL/kg of bodyweight/hour.

For treatment of Multifocal Motor Neuropathy (MMN), Human normal immunoglobulin should be infused intravenously at an initial rate of 0.5 mL/kg BW/hr. If well tolerated, the rate of administration may gradually be increased to a maximum rate of 5.4 mL/kg BW/hr.

Overdose:

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

If you have taken too much GAMMAGARD LIQUID, contact your healthcare provider, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Take GAMMAGARD LIQUID at the earliest available opportunity.

SIDE EFFECTS

What are possible side effects from using GAMMAGARD LIQUID?

These are not all the possible side effects you may feel when taking GAMMAGARD LIQUID. If you experience any side effects not listed here, contact your healthcare professional. Like all medicines, GAMMAGARD LIQUID can have side effects. However, possible side effects may be reduced by slowing the infusion rate.

- General reactions such as chills, headaches, fever, vomiting, allergic reactions, nausea, joint pain, low blood pressure and moderate lower back pain have been experienced occasionally.
- Rarely, cases of a sudden fall in blood pressure were observed, and in isolated cases allergic reactions (anaphylactic shock), even in patients who have shown no reactions to previous infusions. Symptoms for an immediate allergic reaction are bronchitis or asthma, flu-like symptoms, pink eye, generalized rash, skin oedema (angiooedema), dizziness and collapse.
- Cases of temporary meningitis (reversible aseptic meningitis), isolated cases of temporary decrease of red blood cells (reversible haemolytic anaemia/haemolysis) and rare cases of eczema-like symptoms (transient cutaneous reactions) have been observed with immunoglobulin products.
- An increase in blood creatinine content and kidney failure has also been observed.
- Very rarely, cases of blood clot formation in the veins (thromboembolic reactions) resulting in cardiac infarction, stroke, lung embolism, and deep vein thrombosis have been reported.
- If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

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

This is not a complete list of side effects. For any unexpected effects while taking GAMMAGARD LIQUID contact your healthcare professional.

HOW TO STORE IT

Keep out of the reach and sight of children.

Refrigeration storage: Store in a refrigerator (2°C – 8°C) for up to **36 months**.

Room temperature storage: Within the first 24 months from the date of manufacture, GAMMAGARD LIQUID may be stored for a single period of up to 12 months at room

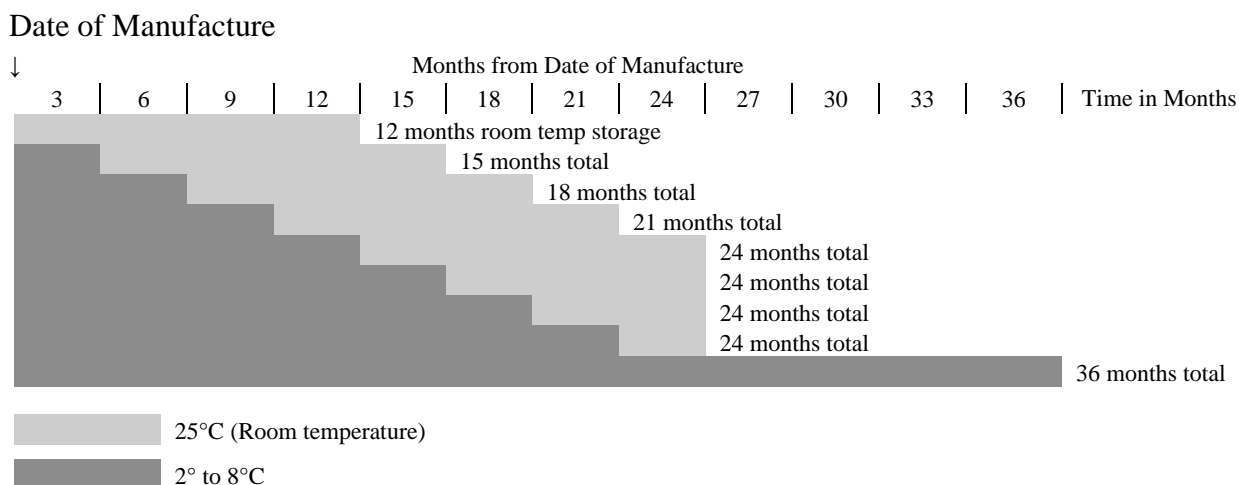
temperature (below 25° C). After this period, unused product must be discarded. See below the detailed storage information.

The total storage time of GAMMAGARD LIQUID depends on the point of the time the vial is transferred to room temperature. Examples for storage times are illustrated in Figure 1. If GAMMAGARD LIQUID is stored at room temperature (below 25° C), the date on which carton is removed from refrigerated storage and the new expiry date must be recorded in the area provided on the carton.

The new expiry date will be the shorter of: 24 months from the date of manufacture (indicated on the carton); or 12 months from the date removed from refrigeration. Once removed from refrigeration and stored at room temperature GAMMAGARD LIQUID must be used or discarded and may not be returned to refrigerated storage.”

Figure 1

Stability Guidelines for GAMMAGARD LIQUID



Example: If the product is taken out of the refrigerator after 3 months, it can be stored for 12 months at room temperature, and the total storage time is 15 months.

Do not freeze.

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

Keep the container in the outer carton in order to protect from light.

Reporting Suspected Side Effects

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

- Report online at <http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to:
 - Canada Vigilance Program
 - Health Canada
 - Postal Locator 1908C
 - Ottawa, Ontario
 - K1A 0K9

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

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

MORE INFORMATION

If you want more information about GAMMAGARD LIQUID:

This document plus the full product monograph, prepared for health professionals can be found at: www.takeda.com/en-ca

Or by calling the sponsor, Takeda Canada Inc. at: 1-800-268-2772

This leaflet was prepared by:

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