HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GAMMAPLEX, IMMUNE GLOBULIN INTRAVENOUS (HUMAN), 5% LIQUID

Initial U.S. Approval: 2009

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors (5.2).**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death[1] may occur in predisposed patients with immune globulin intravenous (IGIV) products, including Gammaplex. Renal dysfunction and acute renal failure occur more commonly with IGIV products containing sucrose. Gammaplex does not contain sucrose (5.1).**

For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity (2.3, 5.1).

RECENT MAJOR CHANGES

Boxed Warnings	09/2013
Indications and Usage (1.1, 1.2)	03/2013
Dosage and Administration (2.2)	03/2013
Contraindications (4)	03/2013
Warnings and Precautions (5.1, 5.5, 5.8, 5.10)	03/2013
Warnings and Precautions (5.2)	09/2013

INDICATIONS AND USAGE

Gammaplex is an Immune Globulin Intravenous (Human) 5% Liquid indicated in adults for the treatment of:

- primary humoral immunodeficiency (PI) (1.1).
- chronic immune thrombocytopenic purpura (ITP) (1.2)

DOSAGE AND ADMINISTRATION

Intravenous Use Only

Indication	Dose	Initial infusion rate	Maintenance infusion rate (if tolerated)
PI	300-800 mg/kg (6-16 mL/kg) every 3-4 weeks	0.5 mg/kg/min (0.01 mL/kg/min) for 15 min	Increase to 4 mg/kg/min (0.08 mL/kg/min)
ITP	1 g/kg (20 mL/kg) for 2 consecutive days	0.5 mg/kg/min (0.01 mL/kg/min) for 15 min	Increase to 4 mg/kg/min (0.08 mL/kg/min)

Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gammaplex if renal function deteriorates (2.3, 5.1).

For patients at risk of renal dysfunction, thrombotic events or volume overload, administer Gammaplex at the minimum infusion rate practicable (2.3, 5.1, 5.2, 5.8).

DOSAGE FORMS AND STRENGTHS

Gammaplex is a liquid solution containing 5% IgG (50 mg/mL).

CONTRAINDICATIONS

- History of anaphylactic or severe systemic reactions to human immunoglobulin (4).
- Gammaplex is contraindicated in patients with hereditary intolerance to fructose, also in infants and neonates for whom sucrose or fructose tolerance has not been established (4).
- IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (4).

WARNINGS AND PRECAUTIONS

- Monitor renal function, including blood urea nitrogen (BUN), serum creatinine and urine output in patients at risk of acute renal injury (5.1).
- Thrombotic events may occur. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity (5.2).
- IgA-deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions (5.3).
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy (5.4).
- Aseptic meningitis syndrome may occur, especially with high doses or rapid infusion (5.5).
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to Gammaplex treatments. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI] (5.7).
- Volume overload can occur. Monitor for signs and symptoms (5.8).
- Consider risks and benefits before prescribing the high dose regimen for chronic ITP in patients at risk of thrombosis, hemolysis, acute kidney injury, or volume overload (5).
- Gammaplex is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.9).
- Passive transfer of antibodies may confound serologic testing (5.10).

ADVERSE REACTIONS

- **PI** - The most common adverse reactions reported in > 5% of clinical trial subjects were headache, pyrexia, fatigue, nausea, hypertension, chills, myalgia, pain, and vomiting (6).
- **Chronic ITP** - The most common adverse reactions reported in > 5% of clinical trial subjects were headache, vomiting, nausea, pyrexia, pruritus, dehydration, and arthralgia (6).

To report SUSPECTED ADVERSE REACTIONS, contact BPL Inc. (1-866-398-0825), FDA (1-800-FDA-1088) or www.fda.gov/medwatch

DRUG INTERACTIONS

- Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, e.g. measles, mumps, and rubella (7).
- Therapy with Gammaplex may confound serological testing (7).

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors** *[see Warnings and Precautions (5.2), Patient Counseling Information (17)]*.
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex[1].**
  Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs *[see Warnings and Precautions (5.1)]*. **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose.**

For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Primary Humoral Immunodeficiency (PI) - Gammaplex is an Immune Globulin Intravenous (Human), 5% Liquid indicated for replacement therapy in adults with primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

1.2 Chronic Immune Thrombocytopenic Purpura (ITP) - Gammaplex is indicated for the treatment of adults with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Preparation and Handling

- Gammaplex is a clear or slightly opalescent, colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy or turbid, or if it contains particulate matter.
- Do not freeze, and do not use any solution that has been frozen.
- DO NOT SHAKE.
- Gammaplex should be at room tempeature (up to 25°C [77°F]) at the time of administration.
- Do not use Gammaplex beyond the expiration date on the product label.
- The Gammaplex vial is for single use only. Due to the absence of anti-microbial preservatives, promptly administer Gammaplex after piercing the cap. Dispose of partially used or unused product.
- Infuse Gammaplex using a separate infusion line.
- Do not mix Gammaplex with other intravenous medications (including normal saline) or other IGIV products.
- An infusion pump may be used to control the rate of administration.
- If large doses of Gammaplex are to be administered, several vials may be pooled using aseptic technique. Begin infusion within 2 hours after pooling.

2.2 Recommended Dose

Treatment of Primary Humoral Immunodeficiency

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The recommended dose of Gammaplex for patients with PI is 300 to 800 mg/kg (6 to 16 mL/kg), administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical response. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Treatment of Chronic Immune Thrombocytopenic Purpura

The recommended dose of Gammaplex for patients with ITP is 1 g/kg (20 mL/kg) on 2 consecutive days, providing a total dose of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (i.e. 1 g /kg/ day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload *[see Warnings and Precautions (5)]*. Adequate data on the platelet response to the low dose regimen (e.g. 400 mg/kg per day for 5 consecutive days) are not available for Gammaplex.

2.3 Administration

- Hydrate the patient adequately prior to the initiation of infusion.
- Due to the absence of anti-microbial preservatives, promptly administer Gammaplex after piercing the cap.
- Infuse Gammaplex intravenously using an intravenous infusion set. See Table 1 for recommended infusion rates.

Table 1: Recommended Infusion Rates for Gammaplex

Indication	Initial infusion rate for first 15 minutes	Maintenance infusion rate (if tolerated)
PI or ITP	0.5 mg/kg/min (0.01 mL/kg/min)	Increase gradually every 15 minutes to 4 mg/kg/min (0.08 mL/kg/min)

- Monitor vital signs throughout the infusion.
- Slow or stop the infusion if adverse reactions occur.
- If symptoms subside, the infusion may be resumed at a lower rate that is comfortable for the patient.
- The observation time of patients after Gammaplex administration may vary. If the patient (a) has not received Gammaplex or another IgG product, (b) is switched from an alternative IGIV product or (c) has had a long interval since the previous infusion, prolong the observation time for adverse reactions after Gammaplex infusion.
- Certain severe adverse reactions may be related to the rate of infusion. Slowing or stopping the infusion often allows the reaction to disappear.
- Ensure that patients with pre-existing renal insufficiency are not volume depleted.
- For patients at increased risk of renal dysfunction, thrombotic events, or volume overload, administer Gammaplex at the minimum infusion rate practicable. Consider discontinuing Gammaplex administration if renal function deteriorates *[see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.8)]*.

3 DOSAGE FORMS AND STRENGTHS

Gammaplex is a liquid solution containing 5% IgG (50 mg/mL).

4 CONTRAINDICATIONS

- Gammaplex is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Gammaplex is contraindicated in patients with hereditary intolerance to fructose, also in infants and neonates for whom sucrose or fructose tolerance has not been established.
- Gammaplex is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Renal Dysfunction / Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death[1] may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering Gammaplex. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency, predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age >65 years), administer Gammaplex at the minimum infusion rate practicable *[see Dosage and Administration (2.3)]*.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

5.2 Thrombotic Events

Thrombosis may occur following treatment with immune globulin products, including Gammaplex[1]. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia / markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity *[see Boxed Warning, Dosage and Administration (2.3), Patient Counseling Information (17)]*.

5.3 Hypersensitivity

Severe hypersensitivity reactions may occur *[see Contraindications (4)]*. In case of hypersensitivity, discontinue Gammaplex infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Gammaplex contains trace amounts of IgA (<10 µg/mL) *[see Description (11)]*. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Gammaplex is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction *[see Contraindications (4)]*.

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VSUS4PI

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events[2].

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae[3].

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting *[see Patient Counseling Information (17)]*. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Gammaplex may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis[4]. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported[5]. Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.

The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., ≥ 2 g/kg), given either as a single administration or divided over several days, and non-O blood group[6]. Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV[7], but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI[8]. Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment[9]. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of volume overload.

5.9 Transmissible Infectious Agents

Because Gammaplex is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare providers to **BPL Inc. 1-866-398-0825**.

Before prescribing Gammaplex, the physician should discuss the risks and benefits of its use with the patient *[see Patient Counseling Information (17)]*.

5.10 Laboratory Tests

- After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.
- Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.
- Clinically assess patients with known renal dysfunction, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or those receiving nephrotoxic agents, and monitor as appropriate (BUN, serum creatinine, urine output) during therapy with Gammaplex.
- Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with polycythemia, cryoglobulins, fasting chylomicronemia/markedly high triglycerides, or monoclonal gammopathies.
- Consider measuring hemoglobin or hematocrit at baseline and approximately 36 to 96 hours post infusion in patients at higher risk of hemolysis. If signs and/or symptoms of hemolysis are present after an infusion of Gammaplex, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

6 ADVERSE REACTIONS

Serious adverse reactions (ARs) observed in clinical trial subjects with primary humoral immunodeficiency (PI) were thrombosis and chest pain. *[see Warnings and Precautions (5.2)]*.

Serious ARs observed in clinical trial subjects with immune thrombocytopenic purpura (ITP) were headache, vomiting and dehydration.

The following potential serious ARs are described below and/or elsewhere in the labeling:

- Thrombotic Events *[see Warnings and Precautions (5.2)]*
- Hemolysis *[see Warnings and Precautions (5.6)]*

The most common ARs observed in the PI clinical trial were headache (18 subjects, 36%), pyrexia (8 subjects, 16%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%), pain (4 subjects, 8%), and vomiting (3 subjects, 6%).

The most common ARs observed in the chronic ITP clinical trial were headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%) and arthralgia (2 subjects, 6%).

6.1 Clinical Trials Experience

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

Treatment of Primary Humoral Immunodeficiency

In a multicenter, open-label, non-randomized clinical trial, 50 subjects with primary humoral immunodeficiency received doses of Gammaplex ranging from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months *[see Clinical Studies (14.1)]*. Routine premedication was not allowed. Of the 703 infusions administered, 2 (4%) subjects received premedication (antipyretic, antihistamine, or anti-emetic agent) prior to 2 courses of treatment, because of experience with consecutive infusion-related ARs.

Twenty-four subjects (48%) had an AR at some time during the clinical trial that was considered product-related. Of these 24 subjects, three had ARs that were considered definitely related to Gammaplex including headache, pyrexia, tachycardia, chest discomfort, and hypertension. More subjects with the 21-day infusion cycle had at least one AR (14 of 22 subjects, 64%) than subjects with the 28-day infusion cycle (10 of 28 subjects, 36%). The total number of ARs during infusion or within 72 hours of infusion was 237 (a rate of 0.34 ARs per infusion), reflecting that some subjects experienced more than one AR during the observation period. The percentage of Gammaplex infusions with one or more ARs within 72 hours of infusion was 21%. The upper bound of the 1-sided 97.5% confidence interval for this percentage was 24%, which was below the pre-specified upper limit of 40% for this safety endpoint.

The most common ARs observed in this clinical trial were headache (18 subjects, 36%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), pyrexia (6 subjects, 12%), pain (4 subjects, 8%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%) and vomiting (3 subjects, 6%). Two subjects experienced serious ARs (thrombosis and chest pain). Table 2 lists the ARs that occurred in more than 5% of the subjects.

Forty-seven of the 50 subjects enrolled in this clinical trial had a negative direct antiglobulin test (DAT) at baseline. Of these 47 subjects, 4 (9%) developed a positive DAT at some time during the clinical trial. However, no subjects showed evidence of hemolytic anemia.

There was no evidence of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) or parvovirus B19 during this clinical trial.

Table 2: Adverse Reactions (ARs*) Occurring in >5% of Subjects with PI

Adverse Reactions	Subjects (%) PI [n=50]	Infusions (%) PI [n=703]
Headache	18 (36%)	53 (7.5%)
Pyrexia	8 (16%)	10 (1.4%)
Sinusitis	8 (16%)	9 (1.3%)
Fatigue	6 (12%)	9 (1.3%)
Nausea	6 (12%)	7 (1.0%)
Nasal Congestion	5 (10%)	3 (0.4%)
Pain	4 (8%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)
Chills	3 (6%)	5 (0.7%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Muscle spasms	3 (6%)	2 (0.3%)
Myalgia	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)

*Adverse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.

Treatment of Chronic Immune Thrombocytopenic Purpura

In a multicenter, open-label, non-randomized clinical trial, 35 subjects with chronic immune thrombocytopenic purpura were treated with a nominal dose of 1,000 mg/kg on each of two consecutive days (total dose 2,000 mg/kg). Doses of Gammaplex ranged from 482 to 1149 mg/kg on an infusion day. The median total dose per subject was 2035 mg/kg. Pre-medication with antihistamine or analgesic drugs was permitted if required, but corticosteroids were not permitted prior to infusion as pre-medication. Ten subjects received corticosteroids for ITP during the trial and one additional subject received corticosteroids as pre-medication in violation of the protocol. All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment.

Twenty-four subjects (69%) reported at least one AR (103 in total); the most commonly reported being headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%), dehydration (2 subjects, 6%) and arthralgia (2 subjects, 6%). Three subjects experienced a total of five serious ARs. Of the five serious ARs, one subject had three concurrently (vomiting, dehydration and headache) and two subjects each had one serious AR (headache). One of these latter two subjects discontinued from the clinical trial because of the severe headache. Table 3 lists the ARs in more than 5% of subjects.

Based on a review of clinical and laboratory data, 4/35 subjects (11%) with drops in hemoglobin exceeding 2 g/dL following administration of Gammaplex were considered to have experienced suspected treatment-emergent hemolysis. Milder treatment-emergent hemolysis could not be excluded for an additional 7 subjects, giving a total of 11 of 35 subjects (31%) for whom hemolysis could not be excluded (not including an additional two subjects who lacked follow-up testing for hemolysis, so their hemolysis status was considered unassessable). Data for two subjects were consistent with possible intravascular hemolysis, including one subject who may also have had an element of extravascular hemolysis. Nine of the possible hemolysis cases were mild and appeared consistent with possible extravascular hemolysis.

There was no evidence of transmission of HBV, HCV, HIV and parvovirus B19 during this clinical trial.

Table 3: Adverse Reactions (ARs*) Occurring in >5% of Subjects with ITP

Adverse Reactions	Subjects (%) ITP [n=35]	Infusions (%) ITP [n=94]
Headache	12 (34%)	15 (16%)
Vomiting	8 (23%)	9 (9.6%)
Nausea	5 (14%)	5 (5.3%)
Pyrexia	5 (14%)	7 (7.4%)
Pain	2 (6%)	2 (2.1%)
Abdominal pain upper	2 (6%)	2 (2.1%)
Gastritis	2 (6%)	2 (2.1%)
Contusion	2 (6%)	2 (2.1%)
Arthralgia	2 (6%)	2 (2.1%)
Cough	2 (6%)	2 (2.1%)
Anemia	2 (6%)	1 (1.1%)
Ecchymosis	2 (6%)	3 (3.2%)
Pruritus	2 (6%)	2 (2.1%)
Dehydration	2 (6%)	2 (2.1%)
Hypertension	2 (6%)	1 (1.1%)
Neck pain	2 (6%)	1 (1.1%)

* Averse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.

6.2 Postmarketing Experience

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

In addition to the adverse reactions identified in clinical studies *[see Adverse Reactions (6.1)]*, the following adverse reactions have been identified during postmarketing use of Gammaplex:

- *Infusion reactions:* Dizziness, back pain, flushing
- *Respiratory:* Pulmonary embolism, dyspnea
- *Cardiovascular:* Myocardial infarction
- *Integumentary:* Rash, urticaria

The following adverse reactions have been identified during post-marketing use of intravenous immune globulins[9]:

- *Infusion reactions:* hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* pyrexia, rigors

7 DRUG INTERACTIONS

- Transitory rise of the various passively transferred antibodies in the patient's blood after infusion of immunoglobulin may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.
- Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella[10,11]. Inform the immunizing physician of recent therapy with Gammaplex so that appropriate measures may be taken *[see Patient Counseling Information (17)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Gammaplex. It is also not known whether Gammaplex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gammaplex should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation[12].

8.3 Nursing Mothers

Use of Gammaplex has not been evaluated in nursing mothers.

8.4 Pediatric Use

Treatment of Primary Humoral Immunodeficiency

Gammaplex was evaluated in six (6) pediatric patients with primary humoral immunodeficiency (2 between ages of 9 and 10, and 4 between ages 12 and 16). This number of pediatric patients was too small for separate evaluation from the adult patients for safety or efficacy *[see Clinical Studies (14)]*. The indication for treatment of Primary Humoral Immunodeficiency is therefore limited to adults only.

Treatment of Chronic Immune Thrombocytopenic Purpura

Gammaplex was evaluated in three (3) pediatric subjects with chronic immune thrombocytopenic purpura (two aged 6 and one aged 12). This number of pediatric patients was too small for separate evaluation from the adult patients for safety or efficacy *[see Clinical Studies (14)]*. The indication for treatment of Chronic Immune Thrombocytopenic Purpura is therefore limited to adults only.

8.5 Geriatric Use

Use caution when administering Gammaplex to patients age 65 and over who are judged to be at increased risk of developing renal insufficiency or thrombotic events *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*. Do not exceed recommended doses, and administer Gammaplex at the minimum infusion rate practicable.

Eight (8) patients with primary humoral immunodeficiency at or over the age of 65 were included within the clinical evaluation of Gammaplex. This number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy *[see Clinical Studies (14)]*.

10 OVERDOSAGE

Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

11 DESCRIPTION

Gammaplex is a ready to use sterile solution of polyclonal human Immunoglobulin G for intravenous administration that contains sorbitol, glycine and polysorbate 80 as stabilizers. Specifically, Gammaplex contains approximately 5 g normal human immunoglobulin and 5 g D-sorbitol in 100 mL of buffer solution containing: 0.6 g glycine, 0.2 g sodium acetate, 0.3 g sodium chloride and ~5 mg polysorbate 80. Immunoglobulin G purity is >95%, the pH is in the range of 4.8 to 5.1, and osmolality is not less than 240 mOsmol/kg (typically 420 to 500 mOsmol/kg). The distribution of the four IgG subclasses is approximately 64% IgG1, 30% IgG2, 5% IgG3, and 1% IgG4. The content of IgA is lower than 10 µg/mL. The anti-D and anti-A/anti-B hemagglutinin content of the drug product is strictly controlled to specification. Gammaplex contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

Gammaplex is prepared from large pools of human plasma by a combination of cold ethanol fractionation and ion exchange chromatography. Fab functions tested include antigen binding activity, and Fc functions tested include complement activation and rubella antibody-mediated hemolysis.

Gammaplex is manufactured from plasma, obtained from healthy US donors, who have passed viral screening tests. All donors are subjected to medical examinations, laboratory tests, and a review of their medical history before being allowed to donate blood or plasma. All plasma donations are screened for antibody to HIV-1/2 and HCV, and hepatitis B surface antigen (HBsAg). Additional testing of donations is carried out in plasma mini-pools (512 donations per pool) that undergo nucleic acid amplification testing (NAT) for HIV, hepatitis B virus (HBV), HCV, hepatitis A virus (HAV) and Parvovirus B19.

Further testing is carried out on the manufacturing pools for HBsAg, and antibody to HIV-1/2; HCV and Parvovirus B19 are also tested by NAT, with the limit for B19 set to not exceed 10^4 IU B19 DNA per mL plasma.

There are three processing steps specifically designed to remove or inactivate viruses:

1) Solvent/Detergent treatment is targeted to enveloped viruses;

2) A virus filtration step designed to remove small viruses including non-enveloped viruses, on a size exclusion basis; and

3) The terminal low pH incubation step is identified as contributing to the overall viral clearance capacity for enveloped and non-enveloped viruses.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model. Overall virus reduction was calculated only from steps that were mechanistically independent from each other.

In addition, each step was validated to provide robust virus reduction. The table below presents the contribution of each process step to virus reduction and the overall process reduction.

Table 4: Viral Reduction by Process Step

Virus	Type (Envelope/ Genome)	Size (nm)	Process Log_{10} Reduction of Virus (LRV) over manufacturing step: Solvent Detergent	20 nm filtration	Terminal low pH/ elevated temperature incubation	Total LRV
HIV	Env/RNA	80-100	>6.8	I	>6.1	>12.9
SIN	Env/RNA	70	>6.7	6.2	>7.3	>20.2
WNV	Env/RNA	50	>6.4	I	NT	>6.4
BVDV	Env/RNA	40-60	>5.6	I	>6.1	>11.7
IBR	Env/DNA	200	>5.0	I	>6.3	>11.3
HAV	Non-Env/RNA	30	NA	>4.8	1.1	>5.9
EMC	Non-Env/RNA	30	NA	>4.8	2.7	>7.5
CPV	Non-Env/RNA	18-24	NA	3.2	1.4	4.6

HIV: Human immunodeficiency virus
SIN: Sindbis virus, model for hepatitis C virus (HCV)
WNV: West Nile Virus
BVDV: Bovine viral diarrhea virus, model for HCV
IBR: Infectious bovine rhinotracheitis, bovine herpesvirus model for enveloped DNA viruses including hepatitis B
HAV: Hepatitis A virus
EMC: Encephalomyocarditis, model for HAV
CPV: Canine parvovirus, model for human parvovirus B19
NA: Not applicable, solvent detergent step is limited to the inactivation of enveloped viruses
I: Inactivation by the product intermediate precluded the accurate estimation of the removal of these viruses by the filtration step
NT: Not tested
B19: Viral clearance of Human Parvovirus B19 was investigated experimentally at the 20 nm filtration step. The estimated Log reduction Factor obtained was 6.0

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Treatment of Primary Humoral Immunodeficiency - Gammaplex is a replacement therapy for primary humoral immunodeficiency. It acts through a broad spectrum of opsonic and neutralizing IgG antibodies against pathogens and their toxins involving antigen binding and effector functions[13,14]. However, the mechanism of action in PI has not been fully elucidated.

Treatment of Chronic Immune Thrombocytopenic Purpura - The mechanism of action of high doses of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

12.3 Pharmacokinetics

Treatment of Primary Humoral Immunodeficiency

In the clinical trial assessing safety and efficacy in primary humoral immunodeficiency, the pharmacokinetics (PK) of Gammaplex was assessed after administration to 24 subjects on 21- or 28-day infusion cycles. Blood samples for PK analysis were obtained after Infusion 9 for subjects on a 21-day schedule (9 subjects) and after Infusion 7 for subjects on a 28-day schedule (15 subjects), i.e. during the sixth month after initiation of Gammaplex treatment.

The mean dose (range) for those on the 21-day schedule was 476 mg/kg (range: 330 to 721 mg/kg), and 468 mg/kg (range: 324 to 799 mg/kg) for those on the 28-day schedule. Table 5 summarizes the PK parameters of Gammaplex, measured as serum concentrations of total IgG.

Treatment of Chronic Immune Thrombocytopenic Purpura

Although the clinical trial in chronic immune thrombocytopenic purpura did not perform a formal PK analysis, a post-hoc analysis was undertaken using the total IgG levels to confirm exposure of the subjects to the product. As in the PI clinical trial, Table 5 summarizes the PK parameters of Gammaplex measured as serum concentrations of total IgG in subjects with ITP.

Table 5: Pharmacokinetic Parameters of Gammaplex in Subjects with PI and ITP (corrected for baseline concentration)

Indication:	PI		ITP*
Parameter (unit)	21-day Dosing Interval (n=9)	28-day Dosing Interval (n=14)	Dosing (1st treatment course only) (n=30)†‡
	Mean§ (95% confidence intervals)	Mean§ (95% confidence intervals)	Mean§ (95% confidence intervals)
C_{max} (mg/dL)	1060 (867-1290)	1190 (995-1410)	3165 (2870-3490)
T_{max} (hr)	3.70 (2.09-6.56)	3.74 (2.42-5.78)	29.1 (28.8-29.5)
AUC (days*mg/dL)	6292¶ (5083-7750)	8792¶ (7542-10208)	20375 (18167-22875)
Half-Life (days)	6.25 (4.92-7.96)	5.96 (4.96-7.21)	8.54 (7.38-9.88)
Clearance (dL/days/kg)	0.073 (0.061-0.088)	0.053 (0.046-0.061)	0.048 (0.043-0.053)
Volume of Distribution (dL/kg)	0.61 (0.46-0.79)	0.43 (0.39-0.48)	0.59 (0.54-0.65)

*Derived from a pharmacokinetic model to take account of infusions on Days 1 and 2
†Thirty out of 35 subjects were analyzed
‡Data were censored at the time of any retreatment
§Geometric mean
¶AUC_{0-tau}, tau = dosing interval

14 CLINICAL STUDIES

14.1 Treatment of Primary Humoral immunodeficiency

In a Phase 3 multicenter, open-label clinical trial to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex in primary humoral immunodeficiency, 50 subjects on regular IGIV replacement therapy for at least 3 months prior to participation were treated for 12 months at 21-day (22 subjects) or 28-day (28 subjects) dosing intervals. Of the 50 subjects, 26 were male and 24 were female, and 46 were Caucasian. They were in the age range of 9 to 78 years.

Doses ranged from 279 mg/kg to 799 mg/kg. The mean dose (range) for the 21-day interval was 465 mg/kg (330 - 693 mg/kg); the mean dose (range) for the 28-day interval was 458 mg/kg (326 - 790 mg/kg). Subjects received a total of 703 infusions of Gammaplex. The maximum infusion rate allowed during this clinical trial was 0.08 mL/kg/min (4 mg/kg/min).

The efficacy analysis was based on the annual rate of acute serious bacterial infections (aSBIs), defined as pneumonia, bacteremia/ septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis, per subject per year[15]. Other efficacy analyses were based on the annual rate of infections, antibiotic use, days out of work/school/day care or unable to perform normal activities due to illness, and days of hospitalization.

During the 12-month clinical trial period, no serious acute bacterial infections occurred in any subject with an onset date between the first infusion of Gammaplex and the first follow-up visit, inclusive. Thus, the mean event rate of serious, acute, bacterial infections per year was zero (with an upper 1-sided 99% confidence interval of 0.101).

Table 6: Summary of Efficacy Results in Subjects with PI

Clinical Analyses for Efficacy	Number of Subjects	50
	Total Number of Subject Days	16715
Infections	Annual rate of confirmed serious acute bacterial infections* Annual rate of other infections (median)	0 /subject year † 3.07 infections/subject year
Antibiotic use (therapeutic)	Number of subjects (%) Annual rate	40 (80%) 47.2 days/subject year
Out of work/school/day care or unable to perform normal activities due to illness	Number of subjects (%) Number of days (%) Annual rate	23 (46%) 394 (2.36%) 8.73 days/subject year
Hospitalization	Number of subjects (%) Number of days (%) Annual rate	4 (8%) 29 (0.17%) 0.75 days/subject year

Duration of exposure in all tables relating to GMX01 was calculated as the difference between the date of the last visit (first follow-up visit) i.e. approximately 10-14 days following the last dose of Gammaplex and the date of the first Gammaplex infusion (plus one day).
*Defined as pneumonia, bacterial meningitis, bacteremia/septicemia, osteomyelitis/septic arthritis, and visceral abscess.
†Upper 1-sided 99% confidence interval: 0.101

14.2 Treatment of Chronic Immune Thrombocytopenic Purpura

In a Phase 3 multicenter, open-label clinical trial to evaluate the efficacy and safety of Gammaplex in chronic immune thrombocytopenic purpura, of the 35 subjects enrolled from various ethnic groups, 9 were male and 26 were female. The age range was between 6 and 69 years. Subjects received intravenous infusions on two consecutive days (1 course) and then observed for a further 30 days. Individuals were given the option of a further two courses of treatment (if required), where only safety variables were assessed. Doses of Gammaplex ranged from 482 to 1149 mg/kg on Day 1 and Day 2. The median total dose per subject was 2035 mg/kg. Subjects received a total of 94 infusions (48 treatment courses). All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment.

The primary analysis was based on the platelet count achieved by Day 9 after the first course of treatment with Gammaplex, response being defined as a platelet count of 50 x 10^9/L or greater. Response to treatment on or before Day 9 was achieved by 29 of 35 subjects (82.9%), and the one-sided 97.5% lower confidence limit of the response rate was 66.4%, which met the *a priori* success criterion that required it to be greater than 60%.

Efficacy analyses included the duration of response, and changes in the incidences of bleeding or hemorrhage. At Day 32, the median (+ SD) platelet count (24 + [90] x 10^9/L) was still higher than the baseline value, and 11 of 33 subjects (33.3%) continued to show response of platelet counts of 50 x 10^9/L or greater. The median duration of platelet count response for the responders was 10 days.

Table 7: Median Platelet Count (Standard deviation) and Number and Percent of Subjects with a Platelet Count > 50 x 10^9/L during the clinical trial.

Number of days in clinical trial	Day 1	Day 2	Day 3	Day 5	Day 9	Day 14	Day 21	Day 32
Median Platelet count (x 10^9/L) (Std Dev)	12.0 (11.4)	50.0 (36.4)	93.0 (97.3)	121.5 (151.9)	100.5 (201.3)	15.5 (113.0)	30.0 (80.0)	24.0 (89.9)
Number (n/N) and percent of subjects with a platelet count ≥ 50 x10^9/L	0/35 (0.0%)	18/35 (51.4%)	22/32 (68.8%)	25/32 (78.1%)	22/32 (68.8%	11/30 (36.7%)	10/29 (34.5%)	11/33 (33.3%)

Gammaplex infusions given on Days 1 and 2.

There was an increase in platelet counts for the majority of subjects, and an overall reduction in the manifestations of bleeding after treatment compared to baseline (Day 1). Petechiae, hematomas and gastrointestinal, pulmonary and genitourinary bleeds were all either reduced or absent by Day 32.

There were no thromboembolic episodes in the clinical trial; and vital signs, biochemical, hematological and virology tests did not reveal any unexpected pathophysiology or toxicity.

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16 HOW SUPPLIED/STORAGE AND HANDLING

Gammaplex is supplied in a single use, clear Type II glass bottle, closed with a stopper and oversealed with a tamper-evident cap.

The components used in the packaging for Gammaplex are latex free.

The following presentations of Gammaplex are available:

NDC Number	Grams and Fill Size
64208-8234-1	2.5 g in 50 mL
64208-8234-2	5 g in 100 mL
64208-8234-3	10 g in 200 mL

Each vial has a label with a peel-off strip showing the product name and batch number.

When stored between 2 ºC [35.6 ºF] and 25 ºC [77 ºF]), Gammaplex has a shelf life of 24 months.

Keep Gammaplex in its original carton to protect it from light.

DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

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

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Acute chest pain, shortness of breath, leg pain, and swelling of the legs/feet *[see Warnings and Precautions (5.2)]*.
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting *[see Warnings and Precautions (5.5)]*.
- Increased heart rate, fatigue, yellowing of skin or eyes, dark-colored urine *[see Warnings and Precautions (5.6)]*.
- Trouble breathing, chest pain, blue lips or extremities, fever *[see Warnings and Precautions (5.7)]*.

Inform patients that Gammaplex is made from human plasma and may contain infectious agents that can cause disease. While the risk that Gammaplex can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them *[see Warnings and Precautions (5.9)]*.

Inform patients that Gammaplex can interfere with their immune response to live viral vaccines (e.g., measles, mumps, and rubella), and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations *[see Drug Interactions (7)]*.

Instruct patients to immediately report symptoms of thrombosis. These symptoms may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.

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