

PRESCRIBING INFORMATION

GAMUNEX®-C, Immunoglobulin Normal Human 0.1g/mL (10%) Solution for infusion

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including GAMUNEX-C. 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 [5.4]*)**
- **For patients at risk of thrombosis, administer GAMUNEX-C 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 [2.5]*, *Warnings and Precautions [5.4]*)**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable. (see *Warnings and Precautions [5.2]*)**

1 INDICATIONS AND USAGE

- GAMUNEX-C is indicated as replacement therapy of primary immunodeficiency (PI) states in which severe impairment of antibody forming capacity has been shown, such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyper IgM, Wiskott- Aldrich syndrome, and severe combined immunodeficiencies.¹⁻⁴
- GAMUNEX-C is also indicated for Idiopathic Thrombocytopenia Purpura (ITP) to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.^{5,6}
- Treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

2 DOSAGE AND ADMINISTRATION

Preparation and Handling

- Visually inspect GAMUNEX-C for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid.
- **DO not freeze.** Do not use solutions that have been frozen.
- Prior to use, allow the solution to reach ambient room temperature.
- If the packaging shows any signs of tampering, do not use the product.
- The GAMUNEX-C vial is for single use only. GAMUNEX-C contains no preservative. Use any vial that has been entered promptly. Discard partially used vials. Do not store after entry into vial.
- Infuse GAMUNEX-C using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMUNEX-C infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.
- If dilution is required, GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline.
- Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling.

- Avoid simultaneous administration of GAMUNEX-C and Heparin through a single lumen delivery device due to GAMUNEX-C, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX-C was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin. See table below.

Additional Solutions	Dilution	Line Flush	Delivery Device Flush
5% Dextrose in water	Yes	Yes	Yes
0.9% Sodium Chloride	No	Yes	Yes
Heparin	No	No	No

- Do not mix with immune globulin intravenous (IGIV) products from other manufacturers.
- Do not use after expiration date.

2.1 PI

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

Intravenous (IV)

The dose of GAMUNEX-C for patients with PI is 300 mg/kg to 600 mg/kg body weight (3 mL/kg to 6 mL/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

The recommended initial infusion rate is 1 mg/kg/min (0.01 mL/kg/min). If the infusion is well-tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. (*see Warnings and Precautions [5.2, 5.4]*)

If a patient routinely receives a dose of less than 400 mg/kg of GAMUNEX-C every 3 to 4 weeks (less than 4 mL/kg), and is at risk of measles exposure (i.e., traveling to a measles endemic area), administer a dose of at least 400 mg/kg (4 mL/kg) just prior to the expected measles exposure. If a patient has been exposed to measles, a dose of 400 mg/kg (4 mL/kg) should be administered as soon as possible after exposure.

Subcutaneous (SC)

The dose should be individualized based on the patient's clinical response to GAMUNEX-C therapy and serum IgG trough levels. Begin treatment with GAMUNEX-C one week after the patient's last IGIV infusion. See below under "Initial Weekly Dose". Prior to switching treatment from IGIV to GAMUNEX-C, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. See below under "Dose Adjustment".

Establish the initial weekly dose of GAMUNEX-C by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to achieve a systemic serum IgG exposure (Area Under the Concentration-Time Curve [AUC]) not inferior to that of the previous IGIV treatment. If the patient has not been previously treated with IV GAMUNEX-C, convert the monthly IGIV dose (in grams) by multiplying by 1.37, then dividing this dose into weekly doses based on the patient's previous IGIV treatment interval. Monitor the patient's clinical response, and adjust dose accordingly.

Initial Weekly Dose

To calculate the initial weekly dose of subcutaneous administration of GAMUNEX-C, multiply the previous IGIV dose in grams by the dose adjustment factor of 1.37; then divide this by the number of weeks between doses during the patient's IGIV treatment (i.e., 3 or 4).

$$\text{Initial SC dose (in grams)} = \frac{1.37 \times \text{previous IGIV dose (in grams)}}{\text{Number of weeks between IGIV doses}}$$

To convert the GAMUNEX-C dose (in grams) to milliliters (mL), multiply the calculated Initial SC dose (in grams) by 10.

Dose adjustment

Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level. To determine if a dose adjustment may be considered, measure the patient's serum IgG trough level on IGIV and as early as 5 weeks after switching from IGIV to subcutaneous. The target serum IgG trough level on weekly SC treatment is projected to be the last IGIV trough level plus 340 mg/dL. To determine if further dose adjustments are necessary, monitor the patient's IgG trough level every 2 to 3 months.

To adjust the dose based on trough levels, calculate the difference (in mg/dL) of the patient's serum IgG trough level from the target IgG trough level (the last IGIV trough level + 340 mg/dL). Then find this difference in Table 1 and the corresponding amount (in mL) by which to increase or decrease the weekly dose based on the patient's body weight. **However, the patient's clinical response should be the primary consideration in dose adjustment.**

Table 1: Adjustment (\pm mL) of the Weekly Subcutaneous Dose Based on the Difference (\pm mg/dL) From the Target Serum IgG Trough Level

Difference From Target IgG Trough Level (mg/dL)	Body Weight (kg)												
	10	15	20	30	40	50	60	70	80	90	100	110	120
	Dose Adjustment (mL per Week)*												
50	1	1	2	3	3	4	5	6	7	8	8	9	10
100	2	3	3	5	7	8	10	12	13	15	17	18	20
150	3	4	5	8	10	13	15	18	20	23	25	28	30
200	3	5	7	10	13	17	20	23	27	30	33	37	40
250	4	6	8	13	17	21	25	29	33	38	42	46	50
300	5	8	10	15	20	25	30	35	40	45	50	55	60
350	6	9	12	18	23	29	35	41	47	53	58	64	70
400	7	10	13	20	27	33	40	47	53	60	67	73	80
450	8	11	15	23	30	38	45	53	60	68	75	83	90
500	8	13	17	25	33	42	50	58	67	75	83	92	100

* Dose adjustment in mL is based on the slope of the serum IgG trough level response to subcutaneous administration of GAMUNEX-C dose increments (about 6.0 mg/dL per increment of 1 mg/kg per week).

For example, if a patient with a body weight of 70 kg has an actual IgG trough level of 900 mg/dL and the target level is 1,000 mg/dL, this results in a difference of 100 mg/dL. Therefore, increase the weekly dose of subcutaneous dose by 12 mL.

Monitor the patient's clinical response, and repeat the dose adjustment as needed.

Dosage requirements for patients switching to GAMUNEX-C from another Immune Globulin Subcutaneous (IGSC) product have not been studied. If a patient on GAMUNEX-C does not maintain an adequate clinical response or a serum IgG trough level equivalent to that of the previous IGSC treatment, adjust the dose accordingly. For such patients, Table 1 also provides guidance for dose adjustment to achieve a desired IGSC trough level.

2.2 ITP

DO NOT ADMINISTER SUBCUTANEOUSLY (see Warnings and Precautions [5.10])

GAMUNEX-C may be administered at a total dose of 2 g/kg, divided in two doses of 1 g/kg (10 mL/kg) given on two consecutive days or into five doses of 0.4 g/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1 g/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1 g/kg (10 mL/kg) body weight may be withheld.

The high dose regimen (1 g/kg \times 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern. (see Warnings and Precautions [5.8], Clinical Studies [14])

The recommended initial infusion rate is 1 mg/kg/min (0.01 mL/kg/min). If the infusion is well-tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. (see *Warnings and Precautions* [5.2, 5.4])

2.3 CIDP

GAMUNEX-C may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to four consecutive days. GAMUNEX-C may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered over 1 day or divided into two doses of 0.5 g/kg (5 mL/kg) given on two consecutive days, every 3 weeks.

The recommended initial infusion rate is 2 mg/kg/min (0.02 mL/kg/min). If the infusion is well tolerated, the rate may be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min). For patients judged to be at risk for renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable. (see *Warnings and Precautions* [5.2, 5.4])

2.4 Administration

Administer intravenously for PI, ITP and CIDP.

GAMUNEX-C may also be administered subcutaneously for the treatment of PI.

- Administer GAMUNEX-C at room temperature.
- Inspect GAMUNEX-C visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.
- Do not use if turbid and/or if discoloration is observed.

Intravenous

- Use only 18 gauge needles to penetrate the stopper for dispensing product from the 10 mL vial.
- Use 16 gauge needles or dispensing pins only with 25 mL vial sizes and larger.
- Insert needles or dispensing pins only once and be within the stopper area delineated by the raised ring.
- Penetrate the stopper perpendicular to the plane of the stopper within the ring.

GAMUNEX [®] -C vial size	Gauge of needle to penetrate stopper
10 mL	18 gauge
25, 50, 100, 200 mL	16 gauge

- Use promptly any vial that has been opened.
- Discard partially used vials.
- If dilution is required, GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Infuse GAMUNEX-C using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMUNEX-C infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection

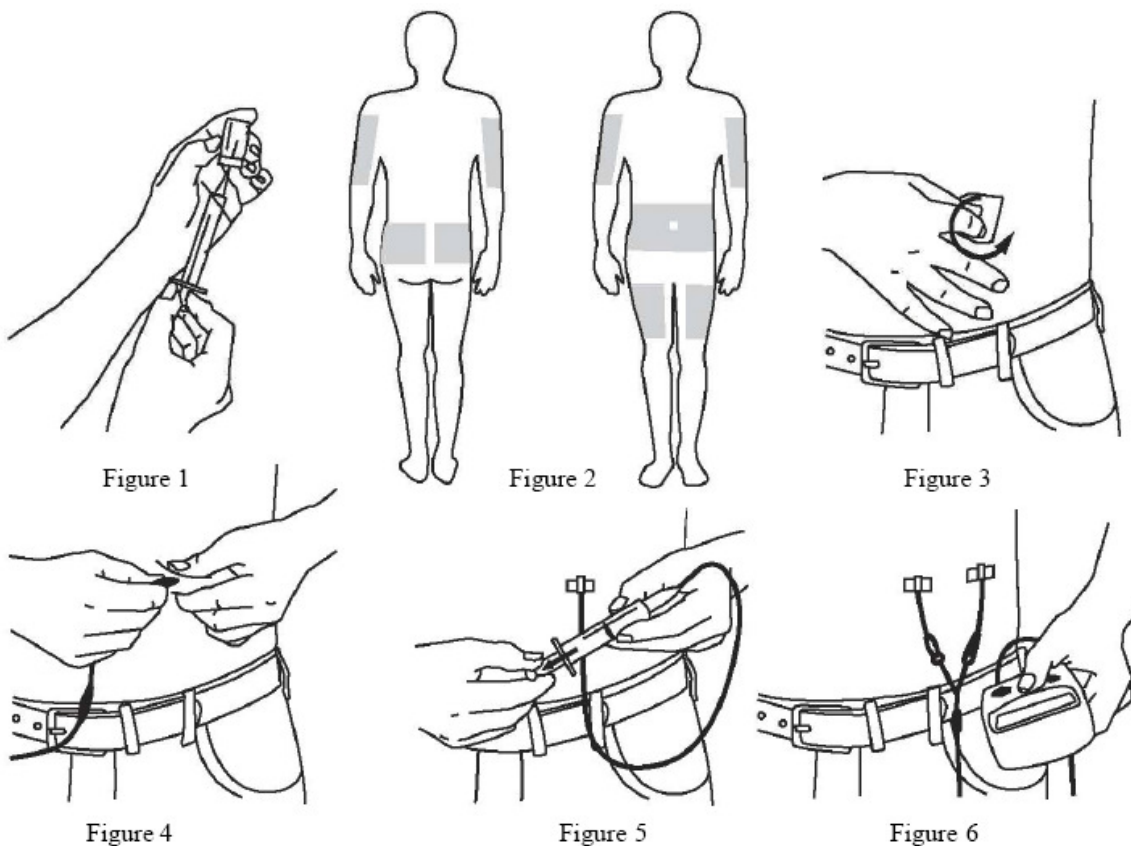
Subcutaneous for PI only

Instructions for Administration

- Prior to use, allow the solution to reach ambient room temperature.
- DO NOT SHAKE.
- Do not use if the solution is cloudy or has particulates.
- Check the product expiration date on the vial. Do not use beyond the expiration date.

1. Use aseptic technique when preparing and administering GAMUNEX-C for injection.
2. Remove the protective cap from the vial to expose the central portion of the rubber stopper. If the packaging shows any sign of tampering, do not use the product.

3. Wipe the rubber stopper with alcohol and allow to dry.
4. Using a sterile syringe and needle, prepare to withdraw GAMUNEX-C by first injecting air into the vial that is equivalent to the amount of GAMUNEX-C to be withdrawn. Then withdraw the desired volume of GAMUNEX-C. If multiple vials are required to achieve the desired dose, repeat this step. (Figure 1)
5. Follow the manufacturer's instructions for filling the pump reservoir and preparing the pump, administration tubing and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with GAMUNEX-C.
6. Select the number and location of injection sites. (Figure 2)
7. Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least two inches apart. (Figure 3)
8. Grasp the skin between two fingers and insert the needle into the subcutaneous tissue. (Figure 4)
9. After inserting each needle, make sure that a blood vessel has not been accidentally entered. Attach a sterile syringe to the end of the primed administration tubing, pull back on the plunger, and if you see blood, remove and discard the needle and administration tubing. (Figure 5)
10. Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site.
11. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
12. Infuse GAMUNEX-C following the manufacturer's instructions for the pump. (Figure 6)



Rate of Administration

Intravenous

Following initial infusion (see table below), the infusion rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg per minute) as tolerated.

Indication	Initial Infusion Rate (first 30 minutes)	Maximum Infusion Rate (if tolerated)
PI	1 mg/kg/min	8 mg/kg/min
ITP	1 mg/kg/min	8 mg/kg/min
CIDP	2 mg/kg/min	8 mg/kg/min

Monitor patient vital signs throughout the infusion. Slow or stop infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

Certain severe adverse drug reactions may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly.

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients at risk of renal dysfunction or thrombosis, administer GAMUNEX-C at the minimum infusion rate practicable and discontinue GAMUNEX-C if renal function deteriorates.

Subcutaneous for PI only

For PI, it is recommended that GAMUNEX-C is infused at a rate of 20 mL/hr per infusion site.

In the SC clinical study, the mean volume administered per infusion site was 34 mL (17-69 mL) and the majority of infusions were administered at a rate of 20 mL/hr per site. Multiple simultaneous infusion sites were enabled by administration tubing and Y-site connection tubing. Most subjects utilized 4 infusion sites per infusion with abdomen and thighs being the most commonly used sites. The maximum number of infusion sites is 8. Injection sites should be at least 2 inches (5 cm) apart.

3 DOSAGE FORMS AND STRENGTH

GAMUNEX-C is a sterile solution for infusion supplied in

- 1 g protein (10 mL),
- 2.5 g protein (25 mL),
- 5 g protein (50 mL),
- 10 g protein (100 mL),
- 20 g protein (200 mL) single-use vials.

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reactions to Immune Globulins or Excipients

GAMUNEX-C is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. Hypersensitivity to any of the excipients .

4.2 IgA Sensitive Patients with History of Hypersensitivity Reaction

GAMUNEX-C is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur with IGIV products, including GAMUNEX-C. In case of hypersensitivity, discontinue GAMUNEX-C infusion immediately and institute appropriate treatment. Have medications such as epinephrine available for immediate treatment of acute hypersensitivity reaction.

GAMUNEX-C contains trace amounts of IgA (average 46 micrograms/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and

anaphylactic reactions. It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity reaction. (see *Contraindications [4]*)

5.2 Renal Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death may occur upon use of IGIV products, especially those containing sucrose.^{7,8} GAMUNEX-C does not contain sucrose. Ensure that patients are not volume depleted prior to the initiation of the infusion of GAMUNEX-C. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, prior to the initial infusion of GAMUNEX-C and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of GAMUNEX-C. For patients judged to be at risk for developing renal dysfunction, including 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, administer GAMUNEX-C at the minimum infusion rate practicable [less than 8 mg/kg/min (0.08 mL/kg/min)]. (see *Dosage and Administration [2.5]*)

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV treatment, including GAMUNEX-C. 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 thrombosis.⁹

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including GAMUNEX-C.¹⁰⁻¹² 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 GAMUNEX-C 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 [2.5]*)

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with IGIV treatment, including GAMUNEX-C. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment. AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu mm, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such symptoms and signs including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

GAMUNEX-C may contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, hemolysis.¹³⁻¹⁶ Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis, has been reported. (see *Adverse Reactions [6]*)

The following risk factors may be related to the development of hemolysis: high doses (e.g., ≥ 2 grams/kg, single administration or divided over several days) and non-O blood group.¹⁷ Underlying inflammatory state in an individual patient may increase the risk of hemolysis, but its role is uncertain.¹⁸

Closely monitor patients for clinical signs and symptoms of hemolysis (*see Warnings and Precautions [5.11]*), particularly patients with risk factors noted above and those with pre-existing anemia and/or cardiovascular or pulmonary compromise. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within approximately 36 hours and again 7 to 10 days post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients following treatment with IGIV products, including GAMUNEX-C.¹⁹ TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

5.9 Transmission of Infectious Agents

Because GAMUNEX-C 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, vCJD or CJD have ever been identified for GAMUNEX-C. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider.

5.10 Hematoma Formation

Do not administer GAMUNEX-C subcutaneously in patients with ITP because of the risk of hematoma formation.

5.11 Monitoring: Laboratory Tests

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

5.12 Interference with Laboratory Tests

After infusion of IgG, 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.

6 ADVERSE REACTIONS

PI: Intravenous: The most common adverse reactions observed at a rate $\geq 5\%$ in subjects with intravenous treatment in the clinical trials were cough increased, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis.

PI: Subcutaneous: The most common adverse reactions observed at a rate $\geq 5\%$ of subjects with subcutaneous treatment in the clinical trials were local infusion site reactions, fatigue, headache, upper respiratory tract infection, arthralgia, diarrhea, nausea, sinusitis, bronchitis, depression, allergic dermatitis, erythema, migraine, myalgia, viral infection, and pyrexia.

ITP: The most common adverse reactions observed at a rate $\geq 5\%$ in subjects in the clinical trials were headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain and dyspepsia.

CIDP: The most common adverse reactions observed at a rate $\geq 5\%$ in subjects in the clinical trial were headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

6.1 Clinical Trials Experience

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

PI: Intravenous Administration

The most serious adverse event observed in clinical study subjects receiving GAMUNEX-C IV for PI was an exacerbation of autoimmune pure red cell aplasia in one subject.

In four different clinical trials to study PI, out of 157 subjects treated with GAMUNEX-C, 4 subjects discontinued due to the following adverse events: Coombs negative hypochromic anemia, autoimmune pure red cell aplasia, arthralgia/hyperhidrosis/fatigue/myalgia/nausea and migraine.

In a study of 87 subjects, 9 subjects in each treatment group were pretreated with non-steroidal medication prior to infusion, such as diphenhydramine and acetaminophen.

Table 2 lists the adverse reactions reported by at least 5% of subjects during the 9-month treatment.

Table 2: Adverse Reactions Occurring in $\geq 5\%$ of Subjects

Adverse Reactions	GAMUNEX®-C No. of subjects: 87 No. of subjects with adverse reaction (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 85 No. of subjects with adverse reaction (percentage of all subjects)
Cough increased	27 (31.0%)	25 (29.4%)
Rhinitis	21 (24.1%)	24 (28.2%)
Headache	13 (14.9%)	17 (20.0%)
Pharyngitis	14 (16.1%)	16 (18.8%)
Asthma	13 (14.9%)	10 (11.8%)
Fever	6 (6.9%)	10 (11.8%)
Nausea	10 (11.5%)	9 (10.6%)
Diarrhea	6 (6.9%)	9 (10.6%)
Sinusitis	5 (5.7%)	6 (7.1%)

*An adverse reaction is an adverse event that meets any of the following 3 criteria: (a) that began during or within 72 hours of the end of product infusion, (b) that was considered at least possibly related by either the investigator or the applicant, and/or (c) whose causality assessment by the investigator was missing or indeterminate.

Table 3 lists the frequency of adverse reactions (as defined for Table 2), which were reported by at least 5% of subjects.

Table 3: Adverse Reactions Frequency

Adverse Reactions	GAMUNEX®-C No. of infusions: 825 Number (percentage of all infusions)	GAMIMUNE® N, 10% No. of infusions: 865 Number (percentage of all infusions)
Cough increased	40 (4.8%)	47 (5.4%)
Rhinitis	34 (4.1%)	44 (5.1%)
Headache	17 (2.1%)	24 (2.8%)
Pharyngitis	20 (2.4%)	24 (2.8%)
Fever	8 (1.0%)	20 (2.3%)
Asthma	17 (2.1%)	12 (1.4%)
Diarrhea	10 (1.2%)	10 (1.2%)
Nausea	10 (1.2%)	10 (1.2%)
Sinusitis	6 (0.7%)	7 (0.8%)

The mean number of adverse reactions per infusion that occurred during or within 72 hours of the end of product infusion was 0.33 for the GAMUNEX-C and 0.39 for the GAMIMUNE® N, 10% [Immune Globulin Intravenous (Human), 10%] treatment group.

In all three trials in primary humoral immunodeficiencies, the maximum infusion rate was 0.08 mL/kg/min (8 mg/kg/min). The infusion rate was reduced for 11 of 222 exposed subjects (7 GAMUNEX-C, 4 GAMIMUNE N, 10%) at 17 occasions. In most instances, mild to moderate hives/urticaria, itching, pain or reaction at infusion site, anxiety or headache was the main reason. There was one case of severe chills. There were no anaphylactic or anaphylactoid reactions to GAMUNEX-C or GAMIMUNE N, 10% in clinical trials.

In the IV efficacy and safety study, serum samples were drawn to monitor the virus safety at baseline and one week after the first infusion of IGIV (for parvovirus B19), eight weeks after first and fifth infusion of IGIV (for hepatitis C, hepatitis B, and HIV-1), 16 weeks after the first and fifth infusion of IGIV (for hepatitis C) and at any time of premature discontinuation of the study (for hepatitis C, hepatitis B, HIV-1, and parvovirus B19). Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, Polymerase Chain Reaction [PCR]) and serological testing. There were no treatment-related emergent findings of virus transmission for either GAMUNEX-C or GAMIMUNE N, 10%.

PI: Subcutaneous Administration (PK and Safety Study)

Adverse reactions were divided into 2 types: 1) Local infusion site reactions, and 2) Non-infusion site adverse reactions. Table 4 lists those adverse reactions (as defined for Table 2) occurring in $\geq 2\%$ of infusions during the SC phase of the pharmacokinetic (PK) crossover and safety trial. [see *Clinical Pharmacology* (12.3)]

Table 4: Most Frequent Adverse Reactions ($\geq 2\%$ of infusions) by Infusion in the SC Phase

Adverse Reactions	Number (Rate[*])
Non-infusion Site Adverse Reactions	
Headache	25 (0.03)
Abdominal Pain	1 (<0.01)
Local Infusion Site Reactions^{†, ‡}	
Mild	389 (0.54)

Moderate	29 (0.04)
Severe	9 (0.01)

* Rate is calculated by the total number of events divided by the number of infusions received (725)

† All local infusion site reactions were *a priori* considered drug-related.

‡ At each level of summation (Preferred Term), local infusion site reactions are counted only once if they occur at the same infusion visit.

Mild – usually transient in nature and generally not interfering with normal activities.

Moderate – sufficiently discomforting to interfere with normal activities.

Severe – prevents normal activities.

Table 5 lists the adverse reactions occurring in $\geq 5\%$ of subjects and the frequency of adverse reactions (as defined for Table 2) per infusion.

Table 5: Most Frequent Adverse Reactions ($\geq 5\%$ of subjects) by Subject and Infusion in the SC phase

Adverse Reaction	No. of Subjects n=32 (%)	No. of Adverse Reactions (Rate*)
Local Infusion Site Reaction†‡	24 (75.0%)	427 (0.59)
Fatigue	5 (15.6%)	6 (0.01)
Headache	4 (12.5%)	25 (0.03)
Upper respiratory tract infection	4 (12.5%)	5 (0.01)
Arthralgia	3 (9.4%)	6 (0.01)
Diarrhea	3 (9.4%)	6 (0.01)
Nausea	3 (9.4%)	4 (0.01)
Sinusitis	3 (9.4%)	4 (0.01)
Bronchitis	2 (6.3%)	2 (<0.01)
Depression	2 (6.3%)	2 (<0.01)
Dermatitis allergic	2 (6.3%)	2 (<0.01)
Erythema	2 (6.3%)	2 (<0.01)
Migraine	2 (6.3%)	2 (<0.01)
Myalgia	2 (6.3%)	2 (<0.01)
Pyrexia	2 (6.3%)	2 (<0.01)
Viral infection	2 (6.3%)	2 (<0.01)

* Rate is calculated by the total number of events divided by the number of infusions received (725)

† All local infusion site reactions were *a priori* considered drug-related

‡ At each level of summation (Preferred Term), infusion site reactions are counted only once if they occur at the same infusion visit.

There were no serious bacterial infections in the SC phase of the PK and safety trial.

Local Infusion Site Reactions

Local infusion site reactions with SC GAMUNEX-C consisted of erythema, pain and swelling. The majority of local infusion site reactions resolved within 3 days. The number of subjects experiencing an infusion site reaction and the number of infusion site reactions decreased over time as subjects received continued weekly SC infusions. At the beginning of the SC phase (week 1), a rate of approximately 1 infusion site reaction per infusion was reported, whereas at the end of the study (week 24) this rate was reduced to 0.5 infusion site reactions per infusion, a reduction of 50%.

ITP

In two different clinical trials to study ITP, out of 76 subjects treated with GAMUNEX-C, 2 subjects discontinued due to the following adverse reactions: Hives and Headache/Fever/Vomiting.

One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX-C. The death was judged to be unrelated to GAMUNEX-C.

No pre-medication with corticosteroids was permitted by the protocol. Twelve ITP subjects treated in each treatment group were pretreated with medication prior to infusion. Generally, diphenhydramine and/or acetaminophen were used. More than 90% of the observed drug-related adverse events were of mild to moderate severity and of transient nature.

The infusion rate was reduced for 4 of the 97 exposed subjects (1 GAMUNEX-C, 3 GAMIMUNE N, 10%) on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons.

Table 6 lists the adverse reactions (as defined for Table 2) reported by at least 5% of subjects during the 3-month efficacy and safety study.

Table 6: Adverse Reactions Occurring in \geq 5% of Subjects

Adverse Reaction	GAMUNEX®-C No. of subjects: 48 Number (percentage of all subjects)	GAMIMUNE® N, 10% No. of subjects: 49 Number (percentage of all subjects)
Headache	25 (52.1%)	26 (53.1%)
Vomiting	6 (12.5%)	8 (16.3%)
Ecchymosis	7 (14.6%)	2 (4.1%)
Fever	6 (12.5%)	6 (12.2%)
Nausea	6 (12.5%)	5 (10.2%)
Rash	4 (8.3%)	0
Abdominal pain	3 (6.3%)	3 (6.1%)
Back pain	3 (6.3%)	2 (4.1%)
Dyspepsia	3 (6.3%)	0
Asthenia	2 (4.2%)	3 (6.1%)
Dizziness	2 (4.2%)	3 (6.1%)

Serum samples were drawn to monitor the virus safety of the ITP subjects at baseline, nine days after the first infusion (for parvovirus B19), and 3 months after the first infusion of IGIV and at any time of premature discontinuation of the study. Viral markers of hepatitis C, hepatitis B, HIV-1, and parvovirus B19 were monitored by nucleic acid testing (NAT, PCR), and serological testing. There were no treatment-related emergent findings of virus transmission for either GAMUNEX®-C, or GAMIMUNE® N, 10%.

CIDP

In the CIDP efficacy and safety study, 113 subjects were exposed to GAMUNEX-C and 95 were exposed to Placebo. (see *Clinical Studies [14]*) As a result of the study design, the drug exposure with GAMUNEX-C was almost twice that of Placebo, with 1096 GAMUNEX-C infusions versus 575 Placebo infusions. Therefore, adverse reactions are reported per infusion (represented as frequency) to correct for differences in drug exposure between the 2 groups. The majority of loading-doses were administered over 2 days. The majority of maintenance-doses were administered over 1 day. Infusions were administered in the mean over 2.7 hours.

Table 7 shows the numbers of subjects per treatment group in the CIDP clinical trial, and the reason for discontinuation due to adverse events:

Table 7: Reasons for Discontinuation Due to Adverse Events:

Number of Subjects		Number of Subjects Discontinued due to Adverse Events	Adverse Event
GAMUNEX [®] -C	113	3 (2.7%)	Urticaria, Dyspnea, Bronchopneumonia
Placebo	95	2 (2.1%)	Cerebrovascular Accident, Deep Vein Thrombosis

The most common adverse reactions with GAMUNEX-C were headache and pyrexia. Table 8 lists adverse reactions (as defined for Table 2) reported by at least 5% of subjects in any treatment group.

Table 8: Adverse Reactions Occurring in ≥ 5% of Subjects

MedDRA Preferred term ^a	GAMUNEX [®] -C No. of subjects: 113			Placebo No. of subjects: 95		
	No. of Subjects (%)	No. of Adverse Reactions	Incidence Density ^b	No. of Subjects (%)	No. of Adverse Reactions	Incidence Density ^b
Headache	35 (31.0%)	50	0.046	7 (7.4%)	9	0.016
Pyrexia	15 (13.3%)	27	0.025	0	0	
Hypertension	10 (8.8%)	19	0.017	3 (3.2%)	3	0.005
Chills	9 (8.0%)	10	0.009	0	0	
Nausea	7 (6.2%)	9	0.008	3 (3.2%)	3	0.005
Rash	7 (6.2%)	10	0.009	1 (1.1%)	1	0.002
Arthralgia	6 (5.3%)	7	0.006	0	0	
Asthenia	6 (5.3%)	6	0.005	1 (1.1%)	2	0.003

^a Reported in ≥5% of subjects in any treatment group.

^b Calculated by the total number of adverse reactions divided by the number of infusions received (1096 for GAMUNEX-C and 575 for Placebo).

The most serious adverse reaction observed in clinical study subjects receiving GAMUNEX-C for CIDP was pulmonary embolism (PE) in one subject with a history of PE.

Laboratory Abnormalities

During the course of the clinical program, ALT and AST elevations were identified in some subjects.

- For ALT, in the IV PI study treatment emergent elevations above the upper limit of normal were transient and observed among 14/80 (18%) of subjects in the GAMUNEX-C group versus 5/88 (6%) of subjects in the GAMIMUNE N, 10% group (p = 0.026).
- In the SC PI study treatment emergent laboratory abnormalities during the SC phase occurred in several subjects. Four subjects (4/32, 13%) had elevated Alkaline Phosphatase. One subject (1/32, 3%) had an elevated ALT and three subjects (3/32, 9%) had an elevated AST. No elevations were >1.6 times the upper limit of normal.
- In the ITP study which employed a higher dose per infusion, but a maximum of only two infusions, the reverse finding for elevation of ALT was observed among 3/44 (7%) of subjects in the GAMUNEX-C group versus 8/43 (19%) of subjects in the GAMIMUNE N, 10% group (p = 0.118).
- In the CIDP study, 15/113 (13%) of subjects in the GAMUNEX-C group and 7/95 (7%) in the Placebo group (p=0.168) had a treatment emergent transient elevation of ALT.

Elevations of ALT and AST were generally mild (<3 times upper limit of normal), transient, and were not associated with obvious symptoms of liver dysfunction.

GAMUNEX-C may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG₄ class. Direct antiglobulin tests (DAT or direct Coombs tests), which are carried out in some centers as a safety check prior to red blood cell transfusions, may become positive temporarily. There were 2 cases of hemolytic anemia across these clinical trials. One hemolytic event not associated with positive DAT findings was observed in the IV PI study in a woman with common variable immune deficiency and B12 deficiency (pernicious anemia) at a dose of 450 mg/kg. The other hemolytic event occurred in the CIDP study in a subject with positive DAT at a dose of 1g/kg.

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 frequencies or establish a causal relationship to product exposure.

The following adverse reactions have been identified during post-approval use of IGIV products^{8,20} including GAMUNEX-C:

- *Infusion Reactions:* Hypersensitivity (e.g., anaphylaxis), tachycardia, malaise, flushing, or other skin reactions, chest discomfort, rigors, and changes in blood pressure
- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures/convulsions, tremor, aseptic meningitis
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis)
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, hemolytic anemia, positive direct antiglobulin (Coombs test)
- *General/Body as a Whole:* Rigors
- *Gastrointestinal:* Hepatic dysfunction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>. Additionally, you can also report to Padagis via the following address: Padagis.co.il.

7 DRUG INTERACTIONS

GAMUNEX-C may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Admixtures of GAMUNEX-C with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMUNEX-C be administered separately from other drugs or medications which the patient may be receiving. The product should not be mixed with IGIVs from other manufacturers.

The infusion line may be flushed before and after administration of GAMUNEX-C with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

Avoid simultaneous administration of GAMUNEX-C and Heparin through a single lumen delivery device due to GAMUNEX-C, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX-C was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin.

Various passively transferred antibodies in immunoglobulin preparations can confound the results of serological testing.

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella. Inform the immunizing physician of recent therapy with GAMUNEX-C so that appropriate measures may be taken.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with GAMUNEX-C use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with GAMUNEX-C. It is not known whether GAMUNEX-C can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX-C should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of GAMUNEX-C in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GAMUNEX-C and any potential adverse effects on the breastfed infant from GAMUNEX-C or from the underlying maternal condition.

8.4 Pediatric Use

PI: Intravenous

GAMUNEX-C was evaluated in 18 pediatric subjects (age range 0-16 years). Twenty-one percent of PI subjects) exposed to GAMUNEX-C were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that vomiting was more frequently reported in pediatrics (3 of 18 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

PI: Subcutaneous

SC GAMUNEX-C was evaluated in only three pediatric subjects (age range 13-15 years) with PI. This number of pediatric subjects was too small for separate evaluation of pharmacokinetics and safety to determine whether they respond differently from adults (*see Clinical Studies [14]*). Efficacy and safety in pediatric patients using the SC route of administration have not been established.

ITP

For treatment of ITP, GAMUNEX-C **must be administered by the intravenous route.**

GAMUNEX-C was evaluated in 12 pediatric subjects with acute ITP. Twenty-five percent of the acute ITP subjects exposed to GAMUNEX-C were children. Pharmacokinetics, safety and efficacy were similar to those in adults with the exception that fever was more frequently reported in pediatrics (6 of 12 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels. One subject, a 10-year-old boy, died suddenly from myocarditis 50 days after his second infusion of GAMUNEX-C. The death was judged to be unrelated to GAMUNEX-C.

CIDP

The safety and effectiveness of GAMUNEX-C have not been established in pediatric subjects with CIDP.

8.5 Geriatric Use

Use caution when administering GAMUNEX-C to patients age 65 and over who are at increased risk for thrombosis or renal insufficiency. (see *Boxed Warning, Warnings and Precautions [5.2,5.4]*) Do not exceed recommended doses, and administer GAMUNEX-C at the minimum infusion rate practicable. Clinical studies of GAMUNEX-C did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10. OVERDOSE

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

11. DESCRIPTION

GAMUNEX-C is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration. GAMUNEX-C is clear to opalescent, and colorless to pale yellow. GAMUNEX-C consists of 9%–11% protein in 0.16–0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. The main component of GAMUNEX-C is IgG ($\geq 98\%$) with a sub-class distribution of IgG₁, IgG₂, IgG₃ and IgG₄ of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively. The distribution of IgG subclasses is similar to that found in normal serum.

GAMUNEX-C also contains water for injection.

GAMUNEX-C contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. GAMUNEX-C doses of 1 g/kg correspond to a glycine dose of 0.15 g/kg. While toxic effects of glycine administration have been reported, the doses and rates of administration were 3–4 fold greater than those for GAMUNEX-C. In another study it was demonstrated that intravenous bolus doses of 0.44 g/kg glycine were not associated with serious adverse effects.²¹ Caprylate is a saturated medium-chain (C8) fatty acid of plant origin. Medium chain fatty acids are considered to be essentially non-toxic. Human subjects receiving medium chain fatty acids parenterally have tolerated doses of 3.0 to 9.0 g/kg/day for periods of several months without adverse effects.²² Residual caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mmol/L). The measured buffer capacity is 35 mEq/L (0.35 mEq/g protein) and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285-295 mOsmol/kg). A dose of 1 g/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45-50 mEq/L of blood, or 3.6 mEq/kg body weight. Thus, the acid load delivered with a dose of 1 g/kg of GAMUNEX-C would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously. The pH of GAMUNEX-C is 4.0–4.5. GAMUNEX-C contains no preservative. GAMUNEX-C is not made with natural rubber latex.

GAMUNEX-C is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. Isotonicity is achieved by the addition of glycine. GAMUNEX-C is incubated in the final container (at the low pH of 4.0 – 4.3). The

product is intended for intravenous administration and may be administered subcutaneously in treatment of PI.

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, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV-2; bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; pseudorabies virus (PRV) as a model for large enveloped DNA viruses (e.g. herpes viruses); Reovirus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.²³

Overall virus reduction was calculated only from steps that were mechanistically independent from each other and truly additive. In addition, each step was verified to provide robust virus reduction across the production range for key operating parameters.

Table9: Log₁₀ Virus Reduction

Process Step	Log ₁₀ Virus Reduction					
	Enveloped Viruses			Non-enveloped Viruses		
	HIV	PRV	BVDV	Reo	HAV	PPV
Caprylate Precipitation / Depth Filtration	C/I*	C/I*	2.7	≥ 3.5	≥ 3.6	4.0
Caprylate Incubation	≥ 4.5	≥ 4.6	≥ 4.5	NA [†]	NA [†]	NA [†]
Depth Filtration [‡]	CAP [§]	CAP [§]	CAP [§]	≥4.3	≥2.0	3.3
Column Chromatography	≥3.0	≥3.3	4.0	≥4.0	≥1.4	4.2
Nanofiltration	≥3.7	M/I	≥ 4.1	≥1.8	M/I	< 1.0
Low pH Incubation	≥6.5	≥4.3	≥5.1	NA [†]	NA [†]	NA [†]
Global Reduction [¶]	≥17.7	≥12.2	≥20.4	≥9.3	≥5.0	8.2

* C/I - Interference by caprylate precluded determination of virus reduction for this step. Although removal of viruses is likely to occur at the caprylate precipitation/depth filtration step, BVDV is the only enveloped virus for which reduction is claimed. The presence of caprylate prevents detection of other, less resistant enveloped viruses and therefore their removal cannot be assessed.

[†] NA - Not Applicable: This step has no effect on non-enveloped viruses.

[‡] Some mechanistic overlap occurs between depth filtration and other steps. Therefore, Grifols Therapeutics LLC has chosen to exclude this step from the global virus reduction calculations.

[§] CAP - The presence of caprylate in the process at this step prevents detection of enveloped viruses, and their removal cannot be assessed.

^{||} M/I - Interference by the process intermediate matrix precluded determination of virus removal capacity for this step.

[¶] Sum of reduction factors greater than or equal to 1 log₁₀.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.²³

Several of the individual production steps in the GAMUNEX-C manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include two depth filtrations (in sequence, a total of ≥ 6.6 log₁₀). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PI

GAMUNEX-C supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacterial, viral, parasitic, and mycoplasmal agents, and their toxins. The mechanism of action in PI has not been fully elucidated.

ITP

The mechanism of action of high doses of immunoglobulins in the treatment of ITP has not been fully elucidated.

CIDP

The precise mechanism of action in CIDP has not been fully elucidated.

12.3 Pharmacokinetics

Intravenous Administration:

Two randomized pharmacokinetic crossover trials were carried out with GAMUNEX-C in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-600 mg/kg body weight per infusion. One trial compared the pharmacokinetic characteristics of GAMUNEX-C to GAMIMUNE N, 10% and the other trial compared the pharmacokinetics of GAMUNEX-C (10% strength) with a 5% concentration of this product. The ratio of the geometric least square means for dose-normalized IgG peak levels of GAMUNEX-C and GAMIMUNE N, 10% was 0.996. The corresponding value for the dose-normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.080 and 1.25. Similar results were obtained in the comparison of GAMUNEX-C 10% to a 5% concentration of GAMUNEX-C.

The main pharmacokinetic parameters of GAMUNEX-C, measured as total IgG in study 100152 are displayed below:

Table 10: PK Parameters of GAMUNEX[®]-C and GAMIMUNE[®] N, 10%

	GAMUNEX [®] -C				GAMIMUNE [®] N, 10%			
	N	Mean	SD	Median	N	Mean	SD	Median
C _{max} (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
C _{max-norm} (kg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC _(0-tn) * (mg*hr/mL)	17	6746.4 8	1348.1 3	6949.47	17	6854.17	1425.08	7119.86
AUC _{(0-tn)norm} * (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
T _{1/2} † (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

* Partial AUC: defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient.

† Only 15 subjects were valid for the analysis of T_{1/2}

The two pharmacokinetic trials with GAMUNEX-C show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels to about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days. IgG trough levels were measured over nine months in the therapeutic equivalence trial. Mean trough levels were 7.8 ± 1.9 mg/mL for the GAMUNEX-C treatment group and 8.2 ± 2.0 mg/mL for the GAMIMUNE N, 10% control group.

PI: Subcutaneous Administration

In a single sequence, open-label, crossover trial, the pharmacokinetics, safety, and tolerability of SC administered GAMUNEX-C in subjects with PI were evaluated. (24) A total of 32 and 26 subjects received GAMUNEX-C as IV or SC for PK study, respectively. Subjects received GAMUNEX-C 200-600 mg/kg IV every 3-4 weeks for at least 3 months, at which time they entered the IV phase of the study. Subjects were crossed over to weekly SC infusions. The weekly SC dose was determined by multiplying the total IV dose by 1.37 and dividing the resultant new total dose by 3 or 4 depending on the previous IV interval. The PK endpoint parameter (AUC of total plasma IgG) following IV and SC administration is summarized below in Table 11. The lower bound of the 90% confidence interval for the geometric mean ratio of AUC (SC vs. IV) was 0.861, therefore, meeting the pre-specified non-inferiority margin between the two modes of administration.

Table 11: Summary of PK Endpoint of AUC

Route of Administration	Statistics	AUC _{0-T,IV} (mg*h/mL)	AUC _{0-T,SC} (mg*h/mL)	Adj. AUC _{0-T,SC} * (mg*h/mL)
IV (n = 32)	Mean	7640	NA	NA
	%CV	15.9		
	Range	5616-10400		
SC (n = 26)	Mean	NA	1947	6858
	%CV		20.4	18.1
	Range		1300-2758	5169-10364

CV, coefficient of variation; NA, not applicable

*Adj. AUC_{0-T,SC}: Adjusted steady-state area under the concentration vs. time curve following SC administration based on IV dosing schedule, calculated as AUC_{0-T,SC} multiplied by 3 or 4 for subjects on every-3-week or every-4-week IV dosing schedule, respectively.

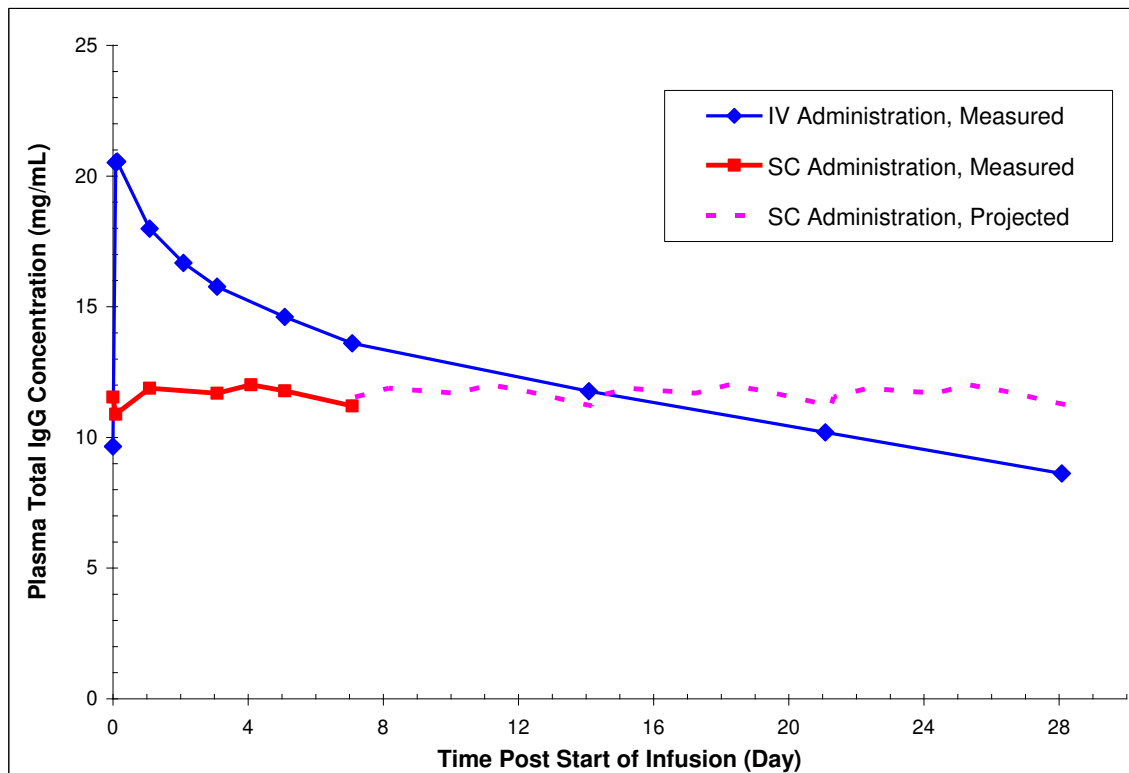
The mean trough concentration (mean C_{trough}) of plasma total IgG following IV and SC administration are presented in Table 12.

Table 12: Mean Plasma Trough Concentrations of Total IgG (mg/mL) in Plasma

	IV Mean C _{trough}	SC Mean C _{trough}
n	32	28
Mean (mg/mL)	9.58	11.4
%CV	22.3	20.4
Range	6.66-14.0	8.10-16.2

In contrast to plasma total IgG levels observed with monthly IV GAMUNEX-C treatment (rapid peaks followed by a slow decline), the plasma IgG levels in subjects receiving weekly SC GAMUNEX-C therapy were relatively stable (Figure 7).

Figure 7: Mean Steady-state Plasma Total IgG Concentration vs. Time Curves Following IV Administration or Weekly SC Administration



14. CLINICAL STUDIES

PI: Intravenous Administration

In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies GAMUNEX-C was demonstrated to be at least as efficacious as GAMIMUNE N, 10% in the prevention of any infection, i.e., validated plus clinically defined, non-validated infections of any organ system, during a nine month treatment period.²⁵ Twenty-six subjects were excluded from the Per Protocol analysis (2 due to non-compliance and 24 due to protocol violations). The analysis for efficacy was based on the annual rate of bacterial infections, pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis.

Table 13: Efficacy Results Per Protocol Analysis

	No. of Subjects with at Least One Infection (%)		Mean Difference (90% Confidence Interval)	p-Value
	GAMUNEX®-C (n=73)	GAMIMUNE® N, 10% (n=73)		
Validated Infections	9 (12%)	17 (23%)	-0.117 (-0.220, -0.015)	0.06
Acute Sinusitis	4 (5%)	10 (14%)		
Exacerbation of Chronic Sinusitis	5 (7%)	6 (8%)		
Pneumonia	0 (0%)	2 (3%)		
Any Infection*	56 (77%)	57 (78%)	-0.020 (-0.135, 0.096)	0.78

* Validated infections plus clinically defined, non-validated infections.

The annual rate of validated infections (Number of Infections/year/subject) was 0.18 in the group treated with GAMUNEX-C and 0.43 in the group treated with GAMIMUNE N, 10% (p=0.023). The annual rates for any infection (validated plus clinically-defined, non-validated infections of any organ system) were 2.88 and 3.38, respectively (p=0.300).

ITP

A double-blind, randomized, parallel group clinical trial with 97 ITP subjects was carried out to test the hypothesis that GAMUNEX-C was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to 20 x10⁹/L to more than 50 x10⁹/L within 7 days after treatment with 2 g/kg IGIV. Twenty-four percent of the subjects were less than or equal to 16 years of age.²⁶

GAMUNEX-C was demonstrated to be at least as effective as GAMIMUNE N, 10% in the treatment of adults and children with acute or chronic ITP.

Table 14: Platelet Response of Per Protocol Analysis

	Number of Responders (percent of all subjects)		Mean Difference (90% Confidence Interval)
	GAMUNEX®-C (n=39)	GAMIMUNE® N, 10% (n=42)	
By Day 7	35 (90%)	35 (83%)	0.075 (-0.037, 0.186)
By Day 23	35 (90%)	36 (86%)	0.051 (-0.058, 0.160)
Sustained for 7 days	29 (74%)	25 (60%)	0.164 (0.003, 0.330)

A trial was conducted to evaluate the clinical response to rapid infusion of GAMUNEX-C in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMUNEX-C on three occasions for treatment of relapses. The infusion rate was randomly assigned to 0.08, 0.11, or 0.14 mL/kg/min (8, 11 or 14 mg/kg/min). Pre-medication with corticosteroids to alleviate infusion-related intolerability was not permitted. Pre-treatment with antihistamines, anti-pyretics and analgesics was permitted. The average dose was approximately 1 g/kg body weight at all three prescribed rates of infusion (0.08, 0.11 and 0.14 mL/kg/min). All patients were administered each of the three planned infusions except seven subjects. Based on 21 patients per treatment group, the a posteriori power to detect twice as many drug-related adverse events between groups was 23%. Of the seven subjects that did not complete the study, five did not require additional treatment, one withdrew because he refused to participate without concomitant medication (prednisone) and one experienced an adverse event (hives); however, this was at the lowest dose rate level (0.08 mL/kg/min).

CIDP

A multi-center, randomized, double-blind, Placebo-controlled trial (The Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified CIDP Efficacy or ICE study) was conducted with GAMUNEX-C.²⁷ This study included two separately randomized periods to assess whether GAMUNEX-C was more effective than Placebo for the treatment of CIDP (assessed in the Efficacy Period for up to 24 weeks) and whether long-term administration of GAMUNEX-C could maintain long-term benefit (assessed in the 24 week Randomized Withdrawal Period).

In the Efficacy Period, there was a requirement for Rescue (crossover) to the alternate study drug if the subject did not improve and maintain this improvement until the end of the 24-week treatment period. Subjects entering the Rescue phase followed the same dosing and schedule as in the Efficacy period. Any subject who was rescued (crossed over) and did not improve and maintain this improvement was withdrawn from the study.

Subjects who completed 24 weeks treatment in the Efficacy period or Rescue phase and responded to therapy were eligible for entry into a double-blind Randomized Withdrawal Period. Eligible subjects were re-randomized to GAMUNEX-C or Placebo. Any subject who relapsed was withdrawn from the study.

The Efficacy Period and the Rescue treatment started with a loading dose of 2 g/kg body weight of GAMUNEX-C or equal volume of Placebo given over 2-4 consecutive days. All other infusions (including the first infusion of the Randomized Withdrawal Period) were given as maintenance doses of 1 g/kg body weight (or equivalent volume of Placebo) every three weeks.

The Responder rates of the GAMUNEX-C and Placebo treatment groups were measured by the INCAT score. The INCAT (Inflammatory Neuropathy Cause and Treatment) scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper [arm disability] and maximum of 5 points for lower [leg disability]) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated).²⁸ At the start of the efficacy portion of the study, the INCAT scores were as

follows: Upper Extremity mean was 2.2 ± 1.0 , and median was 2.0 with a range of 0 to 5; Lower Extremity mean was 1.9 ± 0.9 , and median was 2.0 with a range of 1 to 5; Total Overall Score mean was 4.2 ± 1.4 , and median was 4.0 with a range of 2 to 9. A Responder was defined as a subject with at least 1-point improvement from baseline in the adjusted INCAT score that was maintained through 24 weeks.

More subjects with CIDP responded to GAMUNEX-C: 28 of 59 subjects (47.5%) responded to GAMUNEX-C compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%]; **p=0.006**). The study included both subjects who were IGIV-naïve and subjects who had previous IGIV experience. The outcome was influenced by the group of subjects who experienced prior therapy with IGIV, as shown by the outcomes table, below.

Time to relapse for the subset of 57 subjects who previously responded to GAMUNEX-C was evaluated: 31 were randomly reassigned to continue to receive GAMUNEX-C and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMUNEX-C experienced a longer time to relapse versus subjects treated with Placebo (**p=0.011**). The probability of relapse was 13% with GAMUNEX-C versus 45% with Placebo (hazard ratio, 0.19; 95% confidence interval, 0.05, 0.70).

Table 15: Outcomes in Intent-to-Treat Population Efficacy Period

Efficacy Period	GAMUNEX®-C		Placebo		p-value*
	Responder	Non-Responder	Responder	Non-Responder	
All Subjects	28/59 (47.5%)	31/59 (52.5%)	13/58 (22.4%)	45/58 (77.6%)	0.006
IGIV -Naïve Subjects	17/39 (43.6%)	22/39 (56.4%)	13/46 (28.3%)	33/46 (71.7%)	0.174
IGIV - Experienced Subjects	11/20 (55.0%)	9/20 (45.0%)	0/12 (0%)	12/12 (100%)	0.002

* p-value based on Fisher's exact method

The following table shows outcomes for the Rescue Phase (which are supportive data):

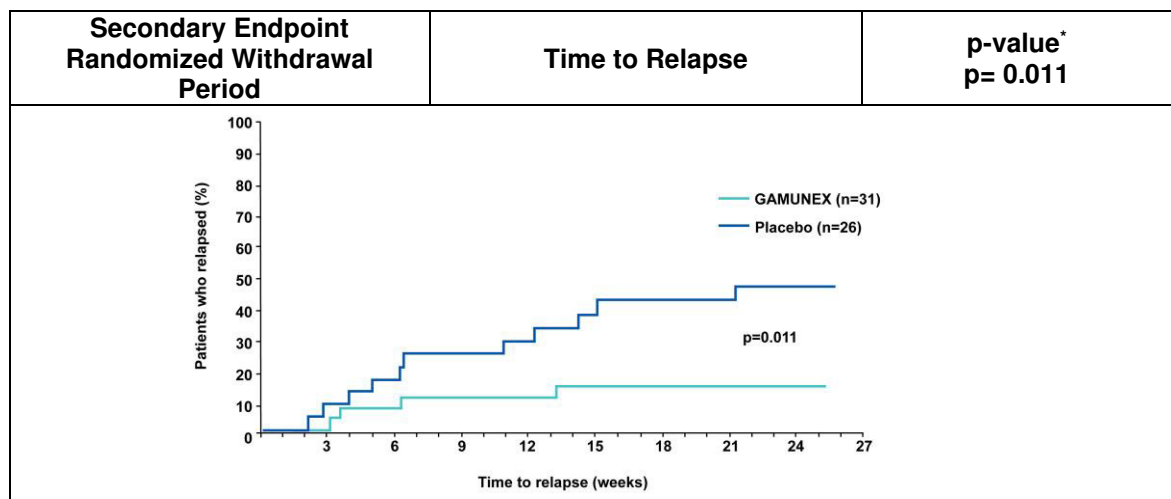
Table 16: Outcomes in Rescue Phase

Rescue Phase	GAMUNEX®-C		Placebo		p-value*
	Success	Failure	Success	Failure	
All Subjects	25/45 (55.6%)	20/45 (44.4%)	6/23 (26.1%)	17/23 (73.9%)	0.038
IGIV- Naïve Subjects	19/33(57.6%)	14/33 (42.4%)	6/18 (33.3%)	12/18 (66.7%)	0.144
IGIV -Experienced Subjects	6/12 (50%)	6/12 (50%)	0/5 (0%)	5/5(100%)	0.102

* p-value based on Fisher's exact method

The following Kaplan-Meier curves show the outcomes for the Randomized Withdrawal Period:

Figure 8: Outcome for Randomized Withdrawal Period



* p-value based on log-rank test

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16. HOW SUPPLIED/STORAGE AND HANDLING

GAMUNEX-C is supplied in single-use, tamper evident vials (shrink band) containing the labeled amount of functionally active IgG. The three larger vial size labels incorporate integrated hangers. GAMUNEX-C is not made with natural rubber latex.

GAMUNEX-C is supplied in the following sizes:

Size	Grams Protein
10 mL	1
25 mL	2.5
50 mL	5
100 mL	10
200 mL	20

- **DO NOT FREEZE**
- Store GAMUNEX-C for up to 36 months at 2 - 8°C from the date of manufacture, and product may be stored at temperature not to exceed 25°C for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded. **If stored outside the refrigerator do not return to the refrigerator.**
- The expiry date of the product is indicated on the packaging materials.
- **Do not use after expiration date.**
- Store in outer packaging to protect from light.

17. Manufactured by

Grifols Therapeutics LLC
North Carolina 27709 USA

18. Registration Holder

Padagis Israel Agencies Ltd.
1 Rakefet St., Shoham

19. Registration number

132-95-31058

Gamunex-C is a registered trademark of Grifols Therapeutics LLC.

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