

GAMMAKED - immune globulin (human) injection

KEDRION BIOPHARMA, INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GAMMAKED™, [Immune Globulin Injection (Human), 10% Caprylate/ Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

See full prescribing information for complete boxed warning.

- Thrombosis may occur with immune globulin products, including GAMMAKED. 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.
- For patients at risk of thrombosis, administer GAMMAKED 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.
- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMMAKED does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer GAMMAKED at the minimum concentration available and the minimum infusion rate practicable. (5.2)

INDICATIONS AND USAGE

GAMMAKED is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older (1.1)
- Idiopathic Thrombocytopenic Purpura (ITP) in adults and children (1.2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults (1.3)

DOSAGE AND ADMINISTRATION

Intravenous Administration Only: ITP and CIDP

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
ITP (2.3)	2 g/kg	1 mg/kg/min	8 mg/kg/min
CIDP (2.4)	loading dose 2 g/kg maintenance dose 1 g/kg	2 mg/kg/min	8 mg/kg/min Every 3 weeks

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

Intravenous or Subcutaneous Administration: PI (2.2)

DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS (5.10)

Route of	Dose*	Initial Infusion Rate	Maintenance
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Administration			Infusion Rate (if tolerated)
Intravenous (IV)	300 - 600 mg/kg	1 mg/kg/min	8 mg/kg/min Every 3 to 4 weeks
Subcutaneous (SC)	1.37 x current IV dose in grams/IV dose interval in weeks	<u>Adult:</u> † 20 mL/hr/site <u>Pediatric:</u> † 10 mL/hr/site (< 25 kg) 15 mL/hr/site (≥ 25 kg)	<u>Adult:</u> † 20 mL/hr/site <u>Pediatric:</u> † 10 mL/hr/site (< 25 kg) 20 mL/hr/site (≥ 25 kg) Weekly

* See section 2.2.

† Adults: use up to 8 infusion sites simultaneously; pediatric: use up to 6 infusion sites simultaneously; for all ages, ensure infusion sites are at least 2 inches (5 cm) apart. (2.5)

-----DOSAGE FORMS AND STRENGTHS-----

GAMMAKED is a sterile solution for injection supplied in 1 g (10 mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), or 20 g (200 mL) single use vials. (3)

-----CONTRAINDICATIONS-----

- Anaphylactic or severe systemic reactions to human immunoglobulin (4.1)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4.2)

-----WARNINGS AND PRECAUTIONS-----

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions. (5.1)
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy. (5.3)
- Aseptic Meningitis Syndrome (AMS) may occur, especially with high doses or rapid infusion. (5.5)
- Hemolysis, either intravascular or due to enhanced RBC sequestration, can develop subsequent to GAMMAKED treatments. Risk factors include high doses and non-O blood group. Closely monitor patients for hemolysis and hemolytic anemia, especially in patients with pre-existing anemia and/or cardiovascular or pulmonary compromise. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]). (5.7)
- Volume overload. (5.8)
- GAMMAKED is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.9)
- GAMMAKED is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMMAKED subcutaneously in patients with ITP. (5.10)
- Passive transfer of antibodies may confound serologic testing. (5.12)

-----ADVERSE REACTIONS-----

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

PI: Intravenous: Cough increased, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis.

Subcutaneous: 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: Headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain and dyspepsia.

CIDP: Headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- The passive transfer of antibodies may transiently interfere with the response to live virus vaccines, such as measles, mumps and rubella. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse

GAMMAKED at the minimum infusion rate practicable. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2020

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including GAMMAKED. 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), Patient Counseling Information (17)]**
- **For patients at risk of thrombosis, administer GAMMAKED 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. GAMMAKED does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMMAKED at the minimum concentration available and the minimum infusion rate practicable. [see Warnings and Precautions (5.2)]**

1 INDICATIONS AND USAGE

GAMMAKED is an immune globulin injection (human) 10% liquid that is indicated for the treatment of:

1.1 Primary Humoral Immunodeficiency (PI)

GAMMAKED is indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.(1-4)

1.2 Idiopathic Thrombocytopenic Purpura (ITP)

GAMMAKED is indicated for the treatment of adults and children with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.(5,6)

1.3 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

GAMMAKED is indicated for the treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Handling

- Visually inspect GAMMAKED 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 and notify Grifols Therapeutics LLC immediately [1-800-520-2807].
- The GAMMAKED vial is for single use only. GAMMAKED contains no preservative. Use any vial that has been entered promptly. Discard partially used vials. Do not store after entry into vial.
- Infuse GAMMAKED using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMMAKED infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.
- If dilution is required, GAMMAKED 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 GAMMAKED and Heparin through a single lumen delivery device due to GAMMAKED, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMMAKED 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	No	Yes	Yes

Chloride			
Heparin	No	No	No

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

2.2 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED therapy and serum IgG trough levels. Begin treatment with GAMMAKED one week after the patient's last IGIV infusion. See below under "Initial Weekly Dose". Prior to switching treatment from IGIV to GAMMAKED, obtain the patient's serum IgG trough level to guide subsequent dose adjustments. See below under "Dose Adjustment".

Establish the initial weekly dose of GAMMAKED 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 GAMMAKED, 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 GAMMAKED, 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 GAMMAKED 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 (±mL) of the Weekly Subcutaneous Dose Based on the Difference (±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 GAMMAKED 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 GAMMAKED from another Immune Globulin Subcutaneous (IGSC) product have not been studied. If a patient on GAMMAKED 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.

2.3 ITP

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

GAMMAKED 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 × 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 GAMMAKED at the minimum infusion rate practicable. [see Warnings and Precautions (5.2, 5.4)]

2.4 CIDP

GAMMAKED 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. GAMMAKED 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. Not all patients may require continued maintenance therapy beyond the initial 6 months of therapy in order to maintain their therapeutic response.

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 GAMMAKED at the minimum infusion rate practicable. [see Warnings and Precautions (5.2, 5.4)]

2.5 Administration

Administer intravenously for PI, ITP and CIDP.

GAMMAKED may also be administered subcutaneously for the treatment of PI.

- Administer GAMMAKED at room temperature.
- Inspect GAMMAKED 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.

GAMMAKED™ 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, GAMMAKED may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Infuse GAMMAKED using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMMAKED infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

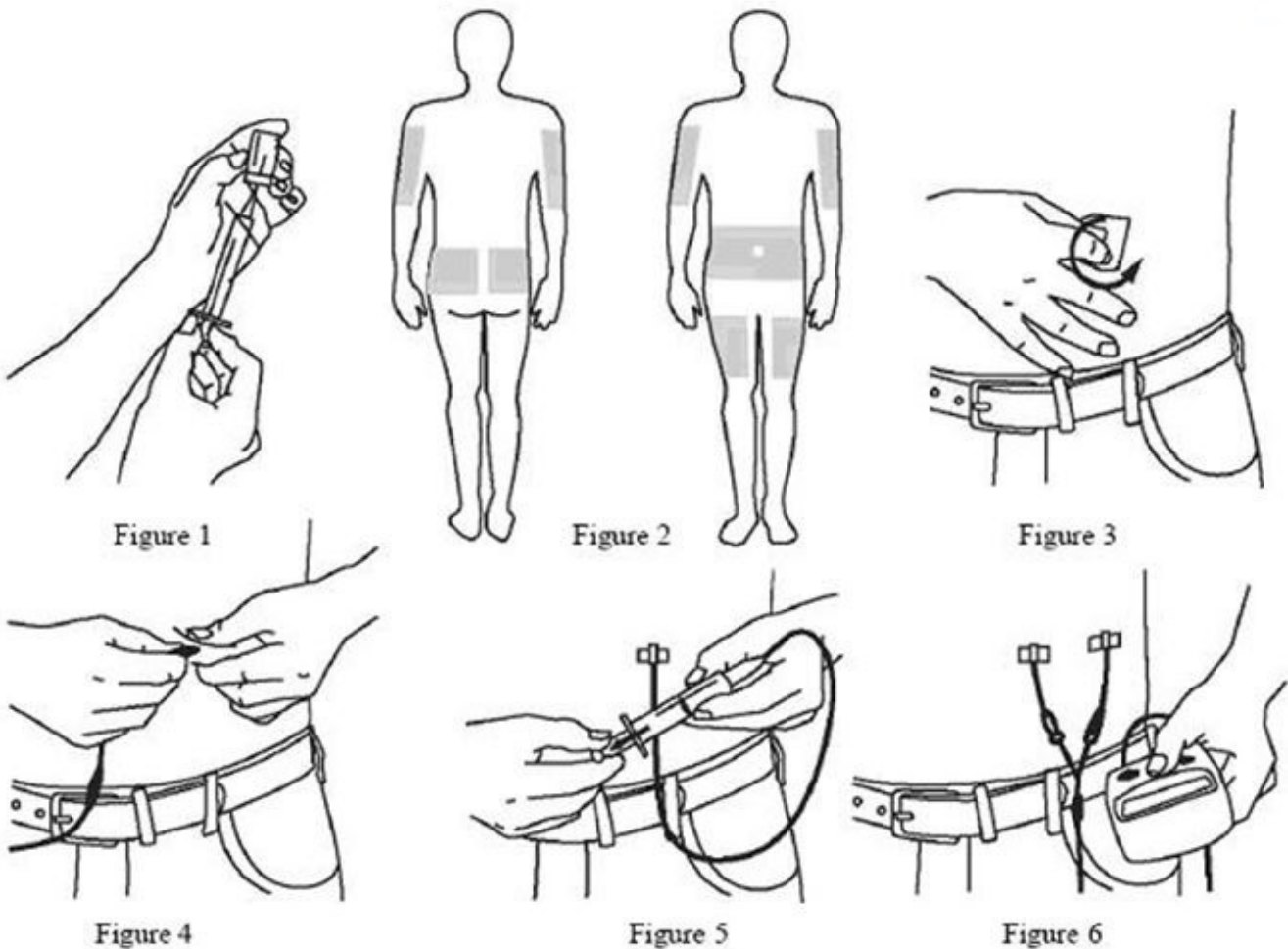
Subcutaneous for PI Only

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 GAMMAKED for injection.
 2. Remove the protective cap from the vial to expose the central portion of the stopper. If the packaging shows any sign of tampering, do not use the product and notify Grifols Therapeutics LLC immediately [1-800-520-2807].
 3. Wipe the stopper with alcohol and allow to dry.
 4. Using a sterile syringe and needle, prepare to withdraw GAMMAKED by first injecting air into the vial that is equivalent to the amount of GAMMAKED to be withdrawn. Then withdraw the desired volume of GAMMAKED. 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 GAMMAKED.

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 GAMMAKED 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 GAMMAKED at the minimum infusion rate practicable and discontinue GAMMAKED if renal function deteriorates.

Subcutaneous for PI Only

For PI, it is recommended that GAMMAKED is infused at a rate of 20 mL per hour per infusion site for adults, and up to 8 infusion sites may be used (most patients used 4 infusion sites). Children and adolescents weighing ≥ 25 kg should start out at a slower infusion rate of 15 mL/hour/infusion site and increase their infusion rate up to 20 mL/hour/infusion site. For children and adolescents weighing < 25 kg, a rate of 10 mL/hour/infusion site is recommended. In children up to 6 infusion sites simultaneously may be used. For patients of all ages ensure that the infusion sites are at least 2 inches (5 cm) apart.

3 DOSAGE FORMS AND STRENGTHS

GAMMAKED is a sterile solution for injection supplied in 1 g protein (10 mL), 2.5 g protein (25 mL), 5 g protein (50 mL), 10 g protein (100 mL), or 20 g protein (200 mL) single use vials.

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reactions to Immune Globulins

GAMMAKED is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

4.2 IgA Sensitive Patients with History of Hypersensitivity Reaction

GAMMAKED 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 GAMMAKED. In case of hypersensitivity, discontinue GAMMAKED infusion immediately and institute appropriate treatment. Have medications such as epinephrine available for immediate treatment of acute hypersensitivity reaction.

GAMMAKED 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) GAMMAKED does not contain sucrose. Ensure that patients are not volume depleted prior to the initiation of the infusion of GAMMAKED. 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 GAMMAKED and again at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of GAMMAKED. [see *Patient Counseling Information (17)*] 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 GAMMAKED 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 GAMMAKED. 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 GAMMAKED.(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 GAMMAKED 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), Patient Counseling Information (17)*]

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with IGIV treatment, including GAMMAKED. 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

GAMMAKED 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 GAMMAKED.(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. [see *Patient Counseling Information (17)*] If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 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 GAMMAKED 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 GAMMAKED. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

5.10 Hematoma Formation

Do not administer GAMMAKED 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 GAMMAKED 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 GAMMAKED, 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 GAMMAKED 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 GAMMAKED, 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	GAMMAKED™ 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	GAMMAKED™	GAMIMUNE® N, 10%
	No. of infusions: 825 Number (percentage of all infusions)	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 GAMMAKED 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 GAMMAKED, 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 GAMMAKED 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 GAMMAKED or GAMIMUNE N, 10%.

PI: Subcutaneous Administration (PK and Safety Studies)

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 two pharmacokinetic (PK) crossover and safety trials, one in adults and adolescents and the other in children and adolescents. [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*)	
	Adult, Adolescent (Study 060001)	Child, Adolescent (Study T5004-401)
Non-infusion Site Adverse Reactions		
Headache	25 (0.03)	1 (0.01)
Abdominal Pain	1 (<0.01)	2 (0.02)
Local Infusion Site Reactions ^{†,‡}		
Mild	389 (0.54)	56 (0.46)
Moderate	29 (0.04)	4 (0.03)
Severe	9 (0.01)	1 (0.01)

* For each trial, rate is calculated by the total number of events divided by the number of infusions received (725 for the adult and adolescent trial and 121 for the children / adolescent trial).

† 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	Adult, Adolescent (Study 060001)		Child, Adolescent (Study T5004-401)	
	No. of Subjects n=32 (%)	No. of Adverse Reactions (Rate*)	No. of Subjects n=11 (%)	No. of Adverse Reactions (Rate*)

Local Infusion Site Reaction ^{†,‡}	24 (75.0%)	427 (0.59)	11 (100%)	61 (0.50)
Fatigue	5 (15.6%)	6 (0.01)	0	0
Headache	4 (12.5%)	25 (0.03)	1 (9.1%)	1 (0.01)
Upper respiratory tract infection	4 (12.5%)	5 (0.01)	1 (9.1%)	1 (0.01)
Arthralgia	3 (9.4%)	6 (0.01)	0	0
Diarrhea	3 (9.4%)	6 (0.01)	0	0
Nausea	3 (9.4%)	4 (0.01)	0	0
Sinusitis	3 (9.4%)	4 (0.01)	0	0
Abdominal pain	1 (3.1%)	1 (<0.01)	1 (9.1%)	2 (0.02)
Abdominal pain upper	0	0	1 (9.1%)	1 (0.01)
Autoimmune thyroiditis	0	0	1 (9.1%)	1 (0.01)
Drug hypersensitivity	0	0	1 (9.1%)	1 (0.01)
Influenza	0	0	1 (9.1%)	1 (0.01)
Oropharyngeal pain	0	0	1 (9.1%)	1 (0.01)
Skin chapped	0	0	1 (9.1%)	1 (0.01)
Viral upper respiratory tract infection	0	0	1 (9.1%)	1 (0.01)
Wheezing	1 (3.1%)	1 (<0.01)	1 (9.1%)	1 (0.01)
Bronchitis	2 (6.3%)	2 (<0.01)	0	0
Depression	2 (6.3%)	2 (<0.01)	0	0
Dermatitis allergic	2 (6.3%)	2 (<0.01)	0	0
	2			

Erythema	2 (6.3%)	2 (<0.01)	0	0
Migraine	2 (6.3%)	2 (<0.01)	0	0
Myalgia	2 (6.3%)	2 (<0.01)	0	0
Pyrexia	2 (6.3%)	2 (<0.01)	0	0
Viral infection	2 (6.3%)	2 (<0.01)	0	0

* For each trial, rate is calculated by the total number of events divided by the number of infusions received (725 for the adult and adolescent trial and 121 for the children / adolescent trial).

† 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 trials.

Local Infusion Site Reactions

Local infusion site reactions with SC GAMMAKED consisted of erythema, pain and swelling. One child discontinued due to infusion site pain. 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) in the adult and adolescent trial, 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%. In the children and adolescent trial, the rate of local infusion site reactions decreased from week 1 for all age groups by the end of the study.

ITP

In two different clinical trials to study ITP, out of 76 subjects treated with GAMMAKED, 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 GAMMAKED. The death was judged to be unrelated to GAMMAKED.

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 GAMMAKED™, 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	GAMMAKED™ 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 GAMMAKED or GAMIMUNE N, 10%.

CIDP

In the CIDP efficacy and safety study, 113 subjects were exposed to GAMMAKED and 95 were exposed to Placebo. [see *Clinical Studies (14)*] As a result of the study design, the drug exposure with GAMMAKED was almost twice that of Placebo, with 1096 GAMMAKED 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
GAMMAKED™	113	3 (2.7%)	Urticaria, Dyspnea, Bronchopneumonia
Placebo	95	2 (2.1%)	Cerebrovascular Accident, Deep Vein Thrombosis

The most common adverse reactions with GAMMAKED 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 \geq 5% of Subjects

MedDRA Preferred Term*	GAMMAKED™ No. of subjects: 113			Placebo No. of subjects: 95		
	No. of Subjects (%)	No. of Adverse Reactions	Incidence density †	No. of Subjects (%)	No. of Adverse Reactions	Incidence density†
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

* Reported in \geq 5% of subjects in any treatment group.

† Calculated by the total number of adverse reactions divided by the number of infusions received (1096 for GAMMAKED and 575 for Placebo).

The most serious adverse reaction observed in clinical study subjects receiving GAMMAKED 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED 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.

GAMMAKED 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 GAMMAKED:

- *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

7 DRUG INTERACTIONS

GAMMAKED may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline. Admixtures of GAMMAKED with other drugs and intravenous solutions have not been evaluated. It is recommended that GAMMAKED 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 GAMMAKED with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

Avoid simultaneous administration of GAMMAKED and Heparin through a single lumen delivery device due to GAMMAKED, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMMAKED 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 GAMMAKED so that appropriate measures may be taken. [*see Patient Counseling Information (17)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with GAMMAKED use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with GAMMAKED. It is not known whether GAMMAKED can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMMAKED 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 GAMMAKED 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 GAMMAKED and any potential adverse effects on the breastfed infant from GAMMAKED or from the underlying maternal condition.

8.4 Pediatric Use

PI: Intravenous

GAMMAKED was evaluated in 18 pediatric subjects (age range 0-16 years). Twenty-one percent of PI subjects exposed to GAMMAKED 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 GAMMAKED was evaluated in three pediatric subjects (age range 13-15 years) with PI along with adults, and separately in a second trial in 11 children and adolescents (age range 2-16 years). Pharmacokinetics and safety were similar to those in adults. No pediatric-specific dose requirements were necessary to achieve circulating IgG levels. Efficacy and safety in pediatric patients under 2 years of age using the SC route of administration have not been established.

ITP

For treatment of ITP, GAMMAKED **must be administered by the intravenous route.**

GAMMAKED was evaluated in 12 pediatric subjects with acute ITP. Twenty-five percent of the acute ITP subjects exposed to GAMMAKED 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 GAMMAKED. The death was judged to be unrelated to GAMMAKED.

CIDP

The safety and effectiveness of GAMMAKED have not been established in pediatric subjects with CIDP.

8.5 Geriatric Use

Use caution when administering GAMMAKED 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 GAMMAKED at the minimum infusion rate practicable. Clinical studies of GAMMAKED did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

With intravenous administration, overdose of GAMMAKED 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

GAMMAKED is a ready-to-use sterile, non-pyrogenic solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration.

GAMMAKED is clear to opalescent, and colorless to pale yellow. GAMMAKED 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 GAMMAKED 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.

GAMMAKED contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. GAMMAKED 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 GAMMAKED. 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 GAMMAKED would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused instantaneously. The pH of GAMMAKED is 4.0–4.5. GAMMAKED contains no preservative. GAMMAKED is not made with natural rubber latex.

GAMMAKED 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. GAMMAKED 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.

Table 9: Log₁₀ Virus Reduction

	Log ₁₀ Virus Reduction
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Process Step	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 GAMMAKED 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

GAMMAKED 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

Two pharmacokinetic crossover trials were carried out with GAMMAKED in 44 subjects with Primary Humoral Immunodeficiency to assess intravenous vs subcutaneous administration. In the first study, a single sequence, open-label, crossover trial in adults and adolescents, the pharmacokinetics, safety, and tolerability of SC administered GAMMAKED in subjects with PI were evaluated.(24) A total of 32 and 26 subjects received GAMMAKED as IV or SC for PK study, respectively, of whom 3 were adolescents. Subjects received GAMMAKED 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.

In the second study, a single sequence, open-label, crossover trial, the pharmacokinetics, safety, and tolerability of SC administered GAMMAKED were evaluated in children and adolescents. The design of the study was essentially the same as above. A total of 11 subjects received GAMMAKED as IV and 10 received GAMMAKED as SC for PK analysis. Age groups were as follows: age 2 to 5 years, [N = 1 both phases]; 6 to 11 years, [N = 5 completing IV phase, N = 4 evaluated in SC phase]; 12-16 years: [N = 5 both phases].

Intravenous Administration

The pharmacokinetic parameters of GAMMAKED, measured as total IgG for intravenous administration are shown in Table 10.

Table 10: PK Parameters Following IV Administration of GAMMAKED™ by Age

Age Group	Statistics	t _{1/2} (hr)	AUC _(0-t) (hr*mg/mL)	AUC _(0-tau) (hr*mg/mL)	CL _(0-t) (mL/hr/kg)	V _{ss} (mL/kg)
2 - 5 years N = 1	Mean	1038.50	7479.0	7499.0	0.05430	82.040
	SD*	NA*	NA*	NA*	NA*	NA*
6 - 11 years N = 5	Mean	758.52	5953.6	6052.6	0.09128	94.784
	SD*	137.989	1573.84	1333.59	0.027465	17.6773
12 - 16 years N = 8	Mean	717.90	8131.9	8009.5	0.07029	73.303
	SD*	170.141	1173.38	1358.76	0.015912	17.2204
≥ 17 years N = 29	Mean	720.62	7564.9	7524.8	0.06243	65.494
	SD*	130.864	1190.68	1183.05	0.015547	18.7172

* SD - standard deviation; NA - not applicable.
Source: Studies 060001, T5004-401

PI: Subcutaneous Administration

The PK parameter (AUC of total IgG) following IV and SC administration is summarized in Table 11 for subcutaneous vs intravenous administration in the two pharmacokinetic trials. In the adult and adolescent trial, 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. The PK analysis results in children and adolescents are consistent to those in the adult and

adolescent trial, demonstrating the appropriateness of the conversion factor of 1.37 applied to calculating the SC dose from the IV dose of GAMMAKED in pediatric populations.

Table 11: Summary of AUC of Total IgG at Steady State Following IV or SC Administration of GAMMAKED™ by Age

Route of Administration	IV (N = 43)			SC (N = 36)	
Age Group (N) Statistics	AUC _{0-τ,IV} (h*mg/mL) (0-21 days)	AUC _{0-τ,IV} (h*mg/mL) (0-28 days)	Adj._AUC _{0-τ,IV} [*] (h*mg/mL) (0-7 days)	AUC _{0-τ,SC} (h*mg/mL) (0-7 days)	AUC Ratio, SC/IV
2-5 years (N)		1	1	1	1
Mean	NC [†]	7498.7	1874.7	2023.0	1.080
%CV	NC [†]	NC [†]	NC [†]	NC [†]	-
Range	NC [†]	NC [†]	NC [†]	NC [†]	NC [†]
6-11 years (N)	5		5	4	4
Mean	6052.7	NC [†]	2017.6	2389.2	1.135
%CV	22%	NC [†]	22%	19%	-
Range	4868 - 8308	NC [†]	1623 - 2769	1971 - 3039	1.10 - 1.21
12-16 years (N)	5	3	8	7	7
Mean	7396.0	9032.0	2387.6	2361.9	0.982
%CV	17%	9%	15%	14%	-
Range	5271 - 8754	8504 - 9950	1757 - 2918	1876 - 2672	0.86 - 1.07
≥ 17 years (N)	10	19	29	24	24
Mean	7424.7	7577.4	2094.5	1899.9	0.882
%CV	14%	17%	20%	20%	-
Range	5781 - 9552	5616 - 10400	1404 - 3184	1300 - 2758	0.70 - 1.04

* Adj._AUC_{0-τ,IV}: Adjusted weekly IV AUC_(0-7 days) is calculated as AUC_(0-21 days)/3 or AUC_(0-28 days)/4.
[†] NC - not calculated
Source: Studies 060001, T5004-401

The mean trough concentrations (mean C_{trough}) of total IgG following IV and SC administration are presented in Table 12 for both studies.

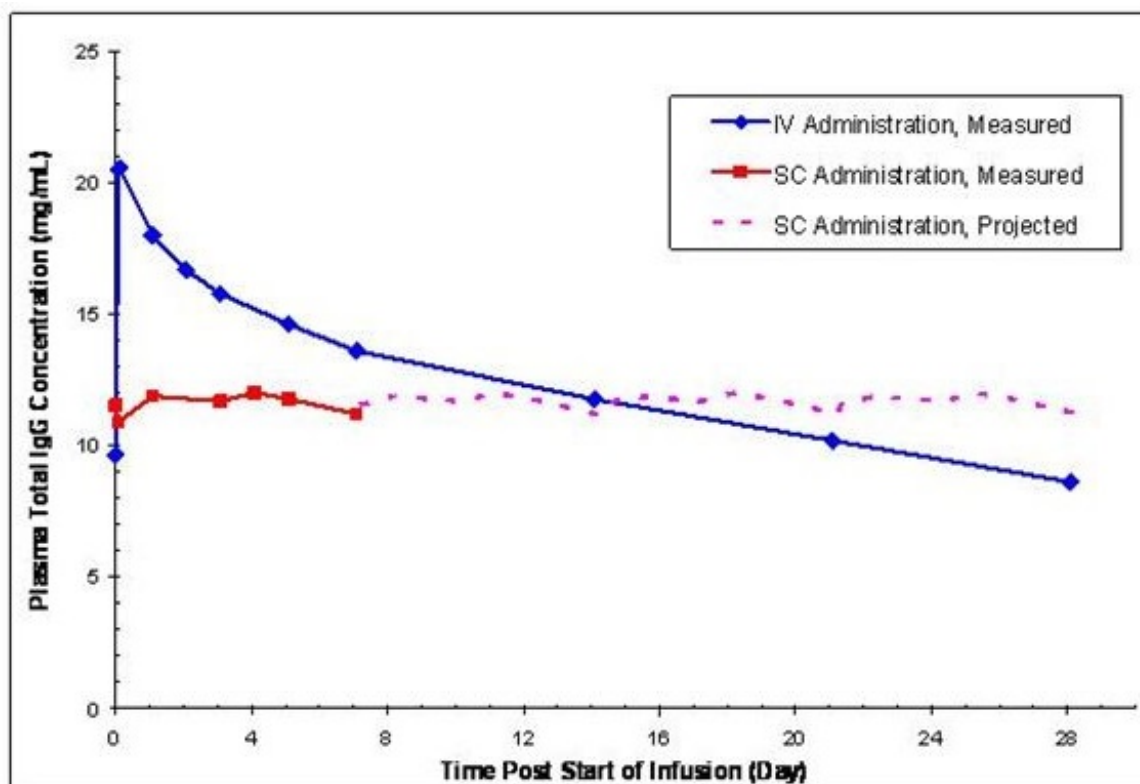
Table 12: Mean Trough Concentrations of Total IgG (mg/mL)

	Adult, Adolescent*		Child, Adolescent [†]	
	IV Mean C _{trough}	SC Mean C _{trough}	IV Mean C _{trough}	SC Mean C _{trough}
n	32	28	11	10
Mean (mg/mL)	9.58	11.4	9.97	13.25
%CV	22.3	20.4	19	14

Range	6.66-14.0	8.10-16.2	7.84-13.20	10.77-16.90
* Measured in plasma; † Measured in serum				

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

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



14 CLINICAL STUDIES

PI: Intravenous Administration

In a randomized, double-blind, parallel group clinical trial with 172 subjects with primary humoral immunodeficiencies GAMMAKED 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
	GAMMAKED™ (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 GAMMAKED 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 GAMMAKED was at least as effective as GAMIMUNE N, 10% in raising platelet counts from less than or equal to $20 \times 10^9/L$ to more than $50 \times 10^9/L$ 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)

GAMMAKED 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)
	GAMMAKED™ (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 GAMMAKED in patients with ITP. The study involved 28 chronic ITP subjects, wherein the subjects received 1 g/kg GAMMAKED 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 GAMMAKED.(27) This study included two separately randomized periods to assess whether GAMMAKED 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED 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 GAMMAKED: 28 of 59 subjects (47.5%) responded to GAMMAKED 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 GAMMAKED was evaluated: 31 were randomly reassigned to continue to receive GAMMAKED and 26 subjects were randomly reassigned to Placebo in the Randomized Withdrawal Period. Subjects who continued to receive GAMMAKED experienced a longer time to relapse versus subjects treated with Placebo (**p=0.011**). The probability of relapse was 13% with GAMMAKED 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	GAMMAKED™		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	GAMMAKED™		Placebo		p-value*
	Success	Failure	Success	Failure	

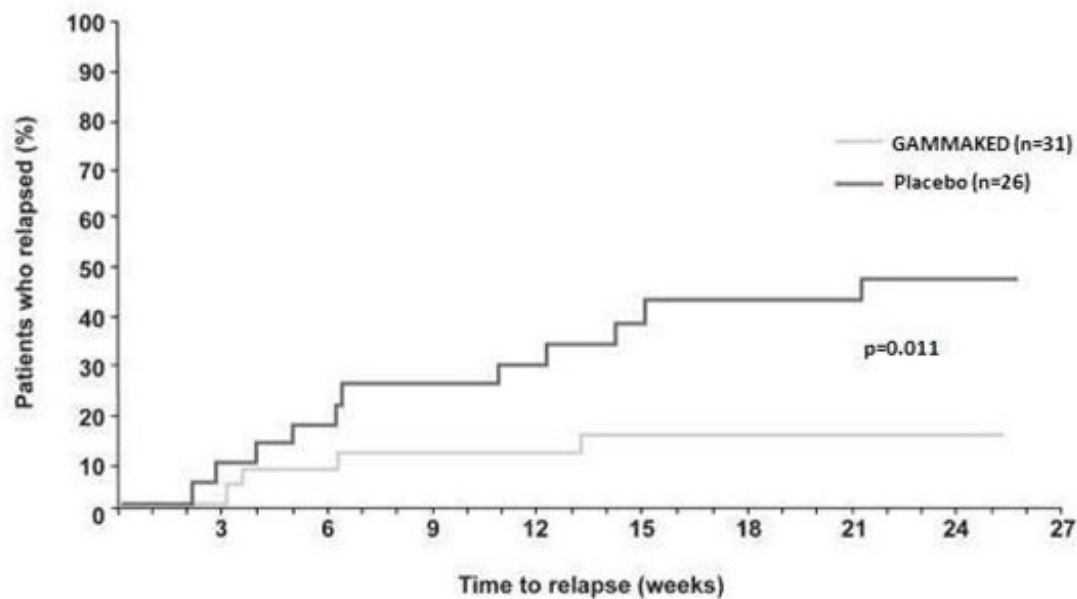
All Subjects	25/45 (55.6%)	20/45 (44.4%)	6/23 (26.1%)	17/23 (73.9%)	0.038
IGIV - Naïve Subjects	19/33 (57.6%)	14/33 (42.4%)	6/18 (33.3%)	12/18 (66.7%)	0.144
IGIV - Experienced Subjects	6/12 (50%)	6/12 (50%)	0/5 (0%)	5/5 (100%)	0.102

* 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

Secondary Endpoint Randomized Withdrawal Period	Time to Relapse	p-value* p= 0.011
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* p-value based on log-rank test

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16 HOW SUPPLIED/STORAGE AND HANDLING

GAMMAKED 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. GAMMAKED is not made with natural rubber latex.

GAMMAKED is supplied in the following sizes:

NDC Number	Size	Grams Protein
76125-900-01	10 mL	1
76125-900-25	25 mL	2.5
76125-900-50	50 mL	5
76125-900-10	100 mL	10
76125-900-20	200 mL	20

- **DO NOT FREEZE**

- Keep the vial in the carton to protect from light.
- GAMMAKED may be stored for 36 months at 2-8°C (36-46°F) from the date of manufacture, AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded.
- Do not use after expiration date.

17 PATIENT COUNSELING INFORMATION

[see Boxed Warning and Warnings and Precautions]

Instruct patients to immediately report the following signs and symptoms to their healthcare provider:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *[see Warnings and Precautions (5.2)]*
- Symptoms of thrombosis which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained

shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body [*see Warnings and Precautions (5.4)*]

- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting [*see Warnings and Precautions (5.5)*]
- Increased heart rate, fatigue, yellowing of the skin or eyes, and dark-colored urine [*see Warnings and Precautions (5.6)*]
- Trouble breathing, chest pain, blue lips or extremities, and fever [*see Warnings and Precautions (5.7)*]

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

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

PI: Self-Administration: Subcutaneous Administration Only

Advise the patient to read the FDA-approved patient labeling (Instructions for Use: Subcutaneous Infusion for Primary Humoral Immunodeficiency).

Provide the patient with instructions on subcutaneous infusion for home treatment, if the physician believes that home administration is appropriate for the patient.

- The type of equipment to be used along with its maintenance,
- proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip),
- maintenance of a treatment diary, and
- measures to be taken in case of adverse reactions in the patient instructions.

Distributed by:

Kedrion Biopharma Inc.

400 Kelby Street
Fort Lee, NJ 07024

Manufactured by:

Grifols Therapeutics LLC

Research Triangle Park, NC 27709 USA
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3054849/3056430

GAMMAKED™

Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified

Instructions for Use: Subcutaneous Infusion for Primary Humoral Immunodeficiency

Information for Patients

Please read this information about GAMMAKED carefully before using this medicine. This information does not take the place of talking with your healthcare professional, and it does not include all of the important information about GAMMAKED. If you have any questions after reading this, contact your healthcare professional.

What is the most important information I should know about GAMMAKED?

GAMMAKED should be infused under your skin (in the subcutaneous tissue). DO NOT inject GAMMAKED into a blood vessel or directly into a muscle.

What is GAMMAKED?

GAMMAKED (găm´-ə-kěd) is an immunoglobulin used to treat primary immune deficiency (PI). Immunoglobulin is another name for the purified antibodies from human plasma that defend the body against infections such as viruses and bacteria. People with PI lack the healthy antibodies needed to fight off these infections. GAMMAKED provides those healthy antibodies and will help lower the number and severity of infections you could get.

Who should NOT take GAMMAKED?

Do not take GAMMAKED if you have known severe allergic reactions or a severe response to Immune Globulin (Human). Tell your doctor if you have had a serious reaction to other medicines that contain immune globulin. Also tell your doctor if you have an immunoglobulin A (IgA) deficiency.

How should I take GAMMAKED?

You will take GAMMAKED through infusions given just below the skin (in the subcutaneous tissue). As directed by your physician, one or more injection sites on your body will be selected. The number and location of the injection sites depends on the amount you need to receive. Typically, adults may use 1 to 4 needles in different locations at one time. You may use up to 8 needles as directed by your doctor. For children, use up to 6 infusion sites simultaneously. For patients of all ages ensure that the infusion sites are at least 2 inches (5 cm) apart. The needles are attached with a tube to the pump. You will need to have infusions once a week.

Instructions for administering GAMMAKED are at the end of this patient Instructions for Use [see "*Steps for Administration*"]. Only use GAMMAKED by yourself after you have been instructed by your doctor or healthcare professional.

What should I avoid while taking GAMMAKED?

Certain types of vaccines (ones containing a live virus) may not work as well for you if you are also receiving immunoglobulin products like GAMMAKED. The antibodies in GAMMAKED may prevent the vaccine from working. Before you get a vaccine, tell the doctor or nurse that you are taking GAMMAKED.

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

What are possible side effects of GAMMAKED?

The most common side effects with GAMMAKED when given under the skin (subcutaneously) are:

- Redness, swelling, and itching at the injection site
- Fatigue
- Headache
- Pain (including pain in the joints, arms, legs)
- Diarrhea
- Nausea
- Migraine
- Fever

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you have any of the following symptoms. They could be signs of a rare, but serious problem.

- Decreased urination, sudden weight gain, fluid retention/swelling in your legs, and/or shortness of breath. They could be signs of a serious kidney problem called renal failure.
- 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. These could be signs of a blood clot in your body (thrombosis). Immediately report symptoms of thrombosis.
- Severe headache, stiff neck, fatigue, fever, sensitivity to light, painful eye movements, nausea and vomiting. These could be signs of a type of brain inflammation called aseptic meningitis.
- Increased heart rate, fatigue, yellow skin or eyes, and dark colored urine. These could be signs of a type of blood problem called hemolytic anemia.
- Chest pains, trouble breathing, blue lips or extremities, and fever. These could be signs of a lung problem called TRALI (transfusion-related acute lung injury).
- Fever over 100°F (37.8°C). This could be a sign of an infection.

Tell your doctor about any side effects that concern you. You can ask your doctor to give you the full prescribing information available to healthcare professionals.

Steps for Administration

Infuse GAMMAKED only after you have been trained by your doctor or healthcare professional. Below are step-by-step instructions to help you remember how to use GAMMAKED. Ask your doctor or healthcare professional about any instructions you do not understand.

Before Using GAMMAKED

- GAMMAKED comes in single-use vials.
- Keep it refrigerated. **Do not let it freeze.**
- Keep the vial in the carton to protect from light.
- GAMMAKED can be stored at room temperature for up to 6 months but you must use it within that time or you must throw it away.

- Do not shake the vials.
- Prior to use, allow the solution to come to room temperature (68-77°F or 20-25°C). This can take 60 minutes or longer.
- Do not use the vial if:
 - the solution is cloudy, discolored or contains particles. The solution should be clear to opalescent, and colorless to pale yellow.
 - the protective cap or plastic shrink band around the cap is missing, or there is any evidence of tampering. Tell your healthcare provider immediately.
 - the expiration date has passed.
- Sanitize your infusion set-up area by preparing a clean, flat, non-porous surface such as a kitchen counter. Avoid using porous surfaces such as wood. Clean the surface with an alcohol wipe using a circular motion from the center outward.

Step 1:

Wash and dry your hands thoroughly before administering GAMMAKED

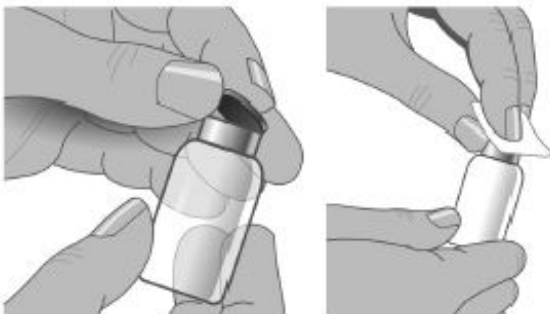
- Your healthcare provider may recommend that you use antibacterial soap or that you wear gloves.



Step 2:

Remove the protective cap and sanitize the stopper

- Remove the protective cap from the vial to expose the central portion of the stopper.
- Wipe the stopper with alcohol and allow to dry.



Step 3:

Use aseptic technique when preparing and administering GAMMAKED

- Do not allow your fingers or other objects to touch the inner stem of the plunger, the syringe tip, or other areas that will come in contact with your GAMMAKED solution. This is called aseptic technique and is designed to prevent transmission of germs.
- Using aseptic technique, attach each needle to the syringe tip.



Step 4:

Prepare the syringe and draw GAMMAKED solution into syringe

- Remove cap from needle.
- Pull the syringe plunger back to the level matching the amount of GAMMAKED to be withdrawn from the vial.
- Place the GAMMAKED vial on a clean flat surface and insert the needle into the center of the vial stopper.
- Inject air into the vial. The amount of air should match the amount of GAMMAKED to be withdrawn.
- Turn the vial upside down and withdraw the correct amount of GAMMAKED. If multiple vials are required to achieve the correct dose, repeat Step 4.



Step 5:

Fill the pump reservoir and prepare the infusion pump

- Follow the pump manufacturer's instructions for filling the pump reservoir and preparing the infusion 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 GAMMAKED. To prime, hold the syringe in one hand and the administration tubing's capped needle in the other. Gently squeeze on the plunger until you see a drop of GAMMAKED exit from the needle.

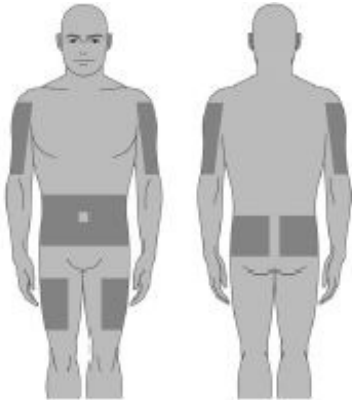
Example Equipment



Step 6:

Select the number and location of infusion sites

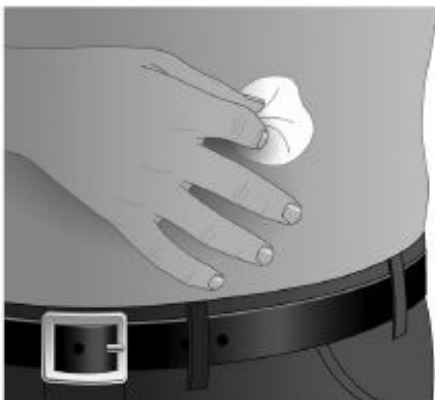
- Select one or more infusion sites as directed by your healthcare provider.
- The number and location of injection sites depends on the volume of the total dose.



Step 7:

Prepare the infusion site

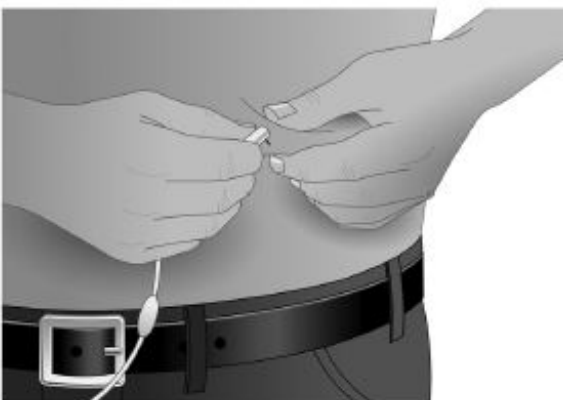
- Cleanse the infusion site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside.
- Sites should be clean, dry, and at least 2 inches apart.



Step 8:

Insert the needle

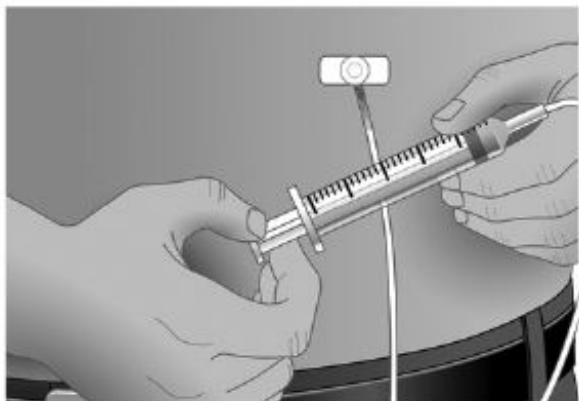
- Grasp the skin between two fingers and insert the needle into the subcutaneous tissue.



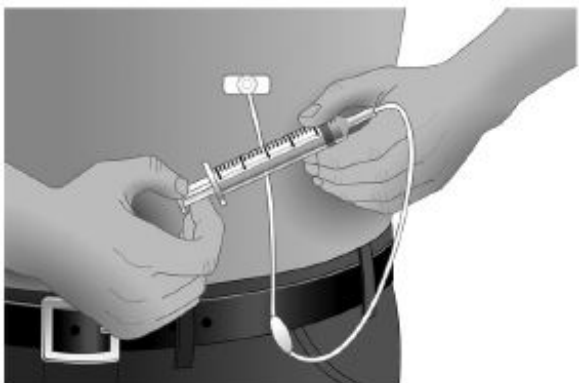
Step 9:

Do not inject GAMMAKED into a blood vessel

- After inserting each needle into tissue (and before your infusion), make sure that a blood vessel has not been accidentally entered. To do this, attach a sterile syringe to the end of the primed administration tubing. Pull back on the syringe plunger and watch for any blood flowing back into administration tubing.
- If you see any blood, remove and discard the needle and administration tubing.



- 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.



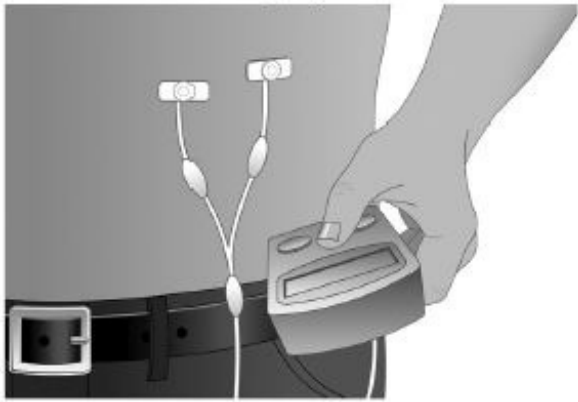
Step 10:

Repeat for other sites, as needed

- If using multiple, simultaneous infusion sites, use Y-site connection tubing and secure to the administration tubing.

Step 11:

Infuse GAMMAKED following the pump manufacturer's instructions for the infusion pump



Step 12:

After infusion, turn off pump and dispose of used supplies

- Follow manufacturer's instructions to turn off pump.
- Undo and discard any dressing or tape.
- Gently remove the inserted needle(s) or catheter(s).
- Discard any unused solution in an appropriate waste container as instructed.
- Discard any used administration equipment in an appropriate waste container.
- Store your supplies in a safe place.
- Follow manufacturer's instructions to care for the infusion pump.

Step 13:

Record each infusion

- Remove the peel-off label with the product lot number from the GAMMAKED vial and use this to complete the patient record.
- Remember to bring your journal with you when you visit your physician or healthcare provider.

Be sure to tell your doctor about any problems you have doing your infusions. Your doctor may ask to see your journal, so be sure to take it with you each time you visit the doctor's office.

Call your doctor for medical advice about side effects. You can also report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Distributed by:

Kedrion Biopharma, Inc.

400 Kelby Street
Fort Lee, NJ 07024

Manufactured by:

Grifols Therapeutics LLC

Research Triangle Park, NC 27709 USA
U.S. License No. 1871

Revised 1/2020

3054849/3056430

PACKAGE LABEL

**Immune Globulin
Injection
(Human), 10%**

gammaked™
caprylate/chromatography purified

Solution for Infusion

10 Grams Protein in 100 ml

NDC 76125-900-10

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

FOR INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION.

Refer to package insert for dosage and administration and compatibility with other solutions.

Single Dose Vial

Do not use if turbid.

Discard unused portion. Do not store after entry into vial.

Contains no preservative

Do not freeze.

Each milliliter (mL) contains approximately 100 mg of protein, not less than 98% of which is immunoglobulin, and approximately 15 mg glycine.

If the shrink band is absent or shows any sign of tampering, do not use the product and notify Grifols Therapeutics LLC immediately.

Not Returnable for Credit or Exchange

Rx only

Manufactured by:

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

Distributed by:
Kedrion Biopharma, Inc.
400 Kelby Street
Fort Lee, NJ 07024

10 Grams Protein in 100 mL

Contents:

One vial of Gammaked

No preservative

Sterile, Non-pyrogenic

Keep the vial in the carton to protect from light.

Gammaked may be stored for 36 months at 2-8°C (36-46°F), AND product may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be immediately used or discarded.

**Date removed
from refrigeration:**

**Immune Globulin
Injection (Human), 10%**

gammaked™
caprylate/chromatography purified

Solution for Infusion

10 Grams Protein in 100 ml

GTIN XXXXXXXXXXXXXXXX
LOT XXXXXXXXXXXX
EXP DDMMMYYYY
SN XXXXXXXXXXXXXXXX

Carton: 3056389



NDC 76125-900-11

Immune Globulin Injection (Human), 10%

gammaked™
caprylate/chromatography purified

Solution for Infusion

10 Grams Protein in 100 ml

Manufactured by: **Grifols Therapeutics LLC**
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

Distributed by: **Kedrion Biopharma, Inc.**
400 Kelby Street, Fort Lee, NJ 07024

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Single Dose Vial
Do not use if turbid.

Rx only

10 Grams Protein in 100 ml

Gammaked

Lot
3053110

Lot
Exp.

10 Grams Protein in 100 ml

NDC 76125-900-11

Immune Globulin Injection (Human), 10%

gammaked™
caprylate/chromatography purified

Solution for Infusion

10 Grams Protein in 100 ml

Manufactured by: Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871
Distributed by: Kedrion Biopharma, Inc.
400 Kelby Street, Fort Lee, NJ 07024

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Single Dose Vial
Do not use if turbid.
Rx only

Gammaked
Lot 3053110
Lot Exp.



GAMMAKED			
immune globulin (human) injection			
Product Information			
Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:76125-900
Route of Administration	INTRAVENOUS, SUBCUTANEOUS		
Active Ingredient/Active Moiety			
	Ingredient Name	Basis of Strength	Strength
	Human Immunoglobulin G (UNII: 66Y330CJHS) (Human Immunoglobulin G - UNII:66Y330CJHS)	Human Immunoglobulin G	10 g in 100 mL
Inactive Ingredients			
	Ingredient Name		Strength
	Glycine (UNII: TE7660XO1C)		
	Water (UNII: 059QF0K00R)		
Product Characteristics			
Color	WHITE (Clear to opalescent liquid, colorless to pale yellow)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			
Packaging			
#	Item Code	Package Description	Marketing Start Date
	NDC:76125		

1	NDC:76125-900-01	1 in 1 CARTON		
1	NDC:76125-900-02	10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:76125-900-25	1 in 1 CARTON		
2	NDC:76125-900-26	25 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
3	NDC:76125-900-50	1 in 1 CARTON		
3	NDC:76125-900-51	50 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
4	NDC:76125-900-10	1 in 1 CARTON		
4	NDC:76125-900-11	100 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
5	NDC:76125-900-20	1 in 1 CARTON		
5	NDC:76125-900-21	200 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125046	10/13/2010	

Labeler - KEDRION BIOPHARMA, INC. (078622209)

Establishment

Name	Address	ID/FEI	Business Operations
GRIFOLS THERAPEUTICS LLC		611019113	manufacture(76125-900)

Revised: 1/2020

KEDRION BIOPHARMA, INC.