

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

INDICATIONS AND USAGE

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

- Primary Humoral Immunodeficiency (PI) (1, 3)
- Idiopathic Thrombocytopenic Purpura (ITP) (2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1, 3)

CONTRAINDICATIONS

- Anaphylactic and systemic reactions to human immunoglobulin (4, 1)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4, 2)

WARNINGS AND PRECAUTIONS

- **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. [1] 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])**

ADVERSE REACTIONS

- **Headache, cough, injection site reaction, nausea, pharyngitis and urticaria.** The most common adverse reactions (≥5%) with subcutaneous use of GAMMAKED were headache, cough, injection site reaction, nausea, pharyngitis and urticaria.
- **Injection site reactions, including hives, urticaria, and pyrexia.** (6, 1)
- **Asymptomatic hemolysis (AMS) has been reported with GAMMAKED and other IGIV treatments, especially with high doses or rapid infusion.** (5, 6)
- **Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.** Monitor patients for hemolysis and hemolytic anemia. (5, 7)
- **Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI], 5, 8)**
- **Volume overload (5, 9)**
- **GAMMAKED is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.** (5, 10)
- **Passive transfer of antibodies may confound serologic testing.** (5, 11)

DRUG INTERACTIONS

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMMAKED were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMMAKED were injection site reactions, headache, fatigue, arthralgia and pyrexia. (6, 1)
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash. (6, 1)
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia. (6, 1)

HOW TO USE GAMMAKED

To report SUSPECTED ADVERSE REACTIONS, contact **Talecris Biotherapeutics, Inc.** at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

HOW TO STORE GAMMAKED

Store GAMMAKED at 20° to 25°C (68° to 77°F) in the original container. Do not freeze. Do not use if the container is cracked, leaking, or the stopper is damaged.

HOW TO PREPARE GAMMAKED

Remove the cap from the vial. Wipe the rubber stopper with alcohol and allow to dry. Use aseptic technique when preparing and administering GAMMAKED for injection.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

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

INDICATIONS AND USAGE

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

- Primary Humoral Immunodeficiency (PI) (1, 3)
- Idiopathic Thrombocytopenic Purpura (ITP) (2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1, 3)

CONTRAINDICATIONS

- Anaphylactic and systemic reactions to human immunoglobulin (4, 1)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4, 2)

WARNINGS AND PRECAUTIONS

- **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. [1] 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])**

ADVERSE REACTIONS

- **Headache, cough, injection site reaction, nausea, pharyngitis and urticaria.** The most common adverse reactions (≥5%) with subcutaneous use of GAMMAKED were headache, cough, injection site reaction, nausea, pharyngitis and urticaria.
- **Injection site reactions, including hives, urticaria, and pyrexia.** (6, 1)
- **Asymptomatic hemolysis (AMS) has been reported with GAMMAKED and other IGIV treatments, especially with high doses or rapid infusion.** (5, 6)
- **Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.** Monitor patients for hemolysis and hemolytic anemia. (5, 7)
- **Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI], 5, 8)**
- **Volume overload (5, 9)**
- **GAMMAKED is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.** (5, 10)
- **Passive transfer of antibodies may confound serologic testing.** (5, 11)

DRUG INTERACTIONS

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMMAKED were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMMAKED were injection site reactions, headache, fatigue, arthralgia and pyrexia. (6, 1)
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash. (6, 1)
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia. (6, 1)

HOW TO USE GAMMAKED

To report SUSPECTED ADVERSE REACTIONS, contact **Talecris Biotherapeutics, Inc.** at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

HOW TO STORE GAMMAKED

Store GAMMAKED at 20° to 25°C (68° to 77°F) in the original container. Do not freeze. Do not use if the container is cracked, leaking, or the stopper is damaged.

HOW TO PREPARE GAMMAKED

Remove the cap from the vial. Wipe the rubber stopper with alcohol and allow to dry. Use aseptic technique when preparing and administering GAMMAKED for injection.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dextrose in water (D5W). Do not dilute with saline.

HOW TO ADMINISTER GAMMAKED

For intravenous use, dilute GAMMAKED with 5% dext

No pre-medication with corticosteroids was permitted by the protocol. Twelve (12) 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™, [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified], 3 GAMMUNE® N, [Immune Globulin Intravenous (Human), 10%] on 4 occasions. Mild to moderate headache, nausea, and fever were the reported reasons.

Table 7 lists any adverse events, irrespective of the causality, reported by at least 5% of subjects during the 3-month efficacy and safety study.

Table 7: Adverse Events Occurring in ≥5% of Subjects Irrespective of Causality

Adverse Event	GAMMAKED™ No. of subjects: 48 No. of subjects with AE (percentage of all subjects)	GAMMUNE® N, 10% No. of subjects: 49 No. of subjects with AE (percentage of all subjects)
Headache	28 (58%)	30 (61%)
Ectchymosis, Purpura	19 (40%)	25 (51%)
Hemorrhage (All systems)	14 (29%)	16 (33%)
Epistaxis	11 (23%)	12 (24%)
Petechiae	10 (21%)	15 (31%)
Fever	10 (21%)	7 (14%)
Vomiting	10 (21%)	10 (20%)
Nausea	10 (21%)	7 (14%)
Thrombocytopenia	7 (15%)	8 (16%)
Accidental injury	6 (13%)	8 (16%)
Rhinitis	6 (13%)	6 (12%)
Pharyngitis	5 (10%)	5 (10%)
Rash	5 (10%)	6 (12%)
Purpitis	4 (8%)	1 (2%)
Asthma	3 (6%)	5 (10%)
Abdominal Pain	3 (6%)	4 (8%)
Arthralgia	3 (6%)	6 (12%)
Back Pain	3 (6%)	3 (6%)
Dizziness	3 (6%)	3 (6%)
Flu Syndrome	3 (6%)	3 (6%)
Neck Pain	3 (6%)	1 (2%)
Anemia	3 (6%)	0 (0%)
Dyspepsia	3 (6%)	0 (0%)

Table 8 lists the adverse reactions reported by at least 5% of subjects during the 3-month efficacy and safety study.

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

Adverse Reaction	GAMMAKED™ No. of subjects: 48 Number (percentage of all subjects)	GAMMUNE® N, 10% No. of subjects: 49 Number (percentage of all subjects)
Headache	24 (50%)	24 (49%)
Vomiting	6 (13%)	8 (16%)
Fever	5 (10%)	5 (10%)
Nausea	5 (10%)	4 (8%)
Back Pain	3 (6%)	2 (4%)
Rash	3 (6%)	0 (0%)

Serum samples were drawn to monitor the viral safety of the ITP subjects at baseline, nine days after the first infusion (for parvovirus B19), and 3 months after the first infusion of IgV 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 viral hepatitis B or hepatitis C either GAMMAKED or GAMMUNE N, 10%.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

In the CIDP efficacy and safety study, 113 subjects were exposed to GAMMAKED and 95 were exposed to Placebo. (see Clinical Studies (14.3)) As a result of the study design, the drug exposure with GAMMAKED was almost twice that of Placebo, with 109% GAMMAKED infusions versus 57% 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 9 shows the numbers of subjects per treatment group in the CIDP clinical trial, and the reason for discontinuation due to adverse events:

Table 9: 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%)
Placebo	95	2 (2.1%)

Table 10 shows adverse events reported by at least 5% of subjects in any treatment group irrespective of causality.

Table 10: Adverse Events Irrespective of Causality Occurring in ≥5% of Subjects

MedDRA Preferred Term ^a	GAMMAKED™		Placebo			
	No. of Subjects (%)	No. of Adverse Events	No. of Subjects (%)	No. of Adverse Events		
Any Adverse Event	85 (75)	377	0.344	45 (47)	120	0.209
Headache	36 (32)	57	0.052	8 (8)	15	0.026
Pyrexia (fever)	15 (13)	27	0.025	0	0	0
Hypertension	10 (9)	20	0.018	4 (4)	6	0.010
Rash	8 (7)	13	0.012	1 (1)	1	0.002
Arthralgia	8 (7)	11	0.010	1 (1)	1	0.002
Asthma	9 (8)	10	0.009	3 (3)	4	0.007
Chills	9 (8)	10	0.009	0	0	0
Back pain	9 (8)	10	0.009	3 (3)	3	0.005
Nausea	7 (6)	9	0.008	3 (3)	3	0.005
Dizziness	7 (6)	3	0.006	1 (1)	1	0.002
Influenza	6 (5)	6	0.005	2 (2)	2	0.003

^a Reported in ≥5% of subjects in any treatment group irrespective of causality.
^b Calculated by the total number of adverse events divided by the number of infusions received (1096 for GAMMAKED and 575 for Placebo).
^c The most common adverse reactions with GAMMAKED were headache and pyrexia. Table 11 lists adverse reactions reported by at least 5% of subjects in any treatment group.

Table 11: Adverse Reactions Occurring in ≥5% of Subjects

MedDRA Preferred Term ^a	GAMMAKED™		Placebo			
	No. of Subjects (%)	No. of Adverse Events	No. of Subjects (%)	No. of Adverse Events		
Any Adverse Reaction	62 (55)	194	0.177	16 (17)	25	0.043
Headache	31 (27)	44	0.040	6 (6)	7	0.012
Pyrexia (fever)	15 (13)	26	0.024	0	0	0
Chills	8 (7)	9	0.008	0	0	0
Hypertension	7 (6)	16	0.015	3 (3)	3	0.005
Rash	6 (5)	8	0.007	1 (1)	1	0.002
Nausea	6 (5)	7	0.006	3 (3)	3	0.005
Asthma	6 (5)	6	0.005	0	0	0

^a Reported in ≥5% of subjects in any treatment group.
^b Calculated by the total number of adverse reactions divided by the number of infusions received (1096 for GAMMAKED and 575 for Placebo).
^c 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 GAMMUNE 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 and one subject (1/32, 3%) had a low 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 was observed among 3/44 (7%) of subjects in the GAMMAKED group versus 8/43 (19%) of subjects in the GAMMUNE 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 IgG₂ 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. Hemolytic events not associated with positive DAT findings were observed in clinical trials.

6.2 Postmarketing Experience
 Because adverse reactions are voluntary and 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.
 GAMMAKED may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG₂ 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. Hemolytic events not associated with positive DAT findings were observed in clinical trials.

GAMMAKED Postmarketing Experience
 The following adverse reactions have been identified and reported during the post marketing use of GAMMAKED:

- Hematology:** Hemolytic anemia
- Infections and Infections:** Aspic meningitis
- The following adverse reactions have been identified and reported during the overall post marketing use of IGIV products [17]:
 - Respiratory:** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
 - Cardiovascular:** Cardiac arrest, thromboembolism, vascular collapse, hypotension
 - Neurological:** Coma, loss of consciousness, seizures/convulsions, tremor

- Integumentary:** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- Hematology:** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs test)
- General/Body as a Whole:** Pyrexia, rigors
- Musculoskeletal:** Back pain
- Gastrointestinal:** Hepatic dysfunction, abdominal pain

7 DRUG INTERACTIONS
 GAMMAKED may be diluted with 5% dextrose in water (D5W). Administers 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 D5W. 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
 Pregnancy Category C. 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. Immune globulin cross the placenta from maternal circulation increasingly after 30 weeks of gestation. [18-19]

8.3 Nursing Mothers
 Use of GAMMAKED has not been evaluated in nursing mothers.

8.4 Pediatric Use
 Treatment of Primary Humoral Immunodeficiency

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 pediatric (3 of 18 subjects). No pediatric-specific dose requirements were necessary to achieve serum IgG levels.

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

Treatment of Idiopathic Thrombocytopenic Purpura
 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 pediatric (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.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy
 The safety and effectiveness of GAMMAKED has 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 judged to be at increased risk for developing thromboembolic events or renal insufficiency. (see Boxed Warning, Warnings and Precautions [5.2]) 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.

11 DESCRIPTION
 GAMMAKED is a ready-to-use sterile solution of human immune globulin protein for intravenous and subcutaneous (PI indication only) administration. GAMMAKED consists of 94%-11% protein in 0.16-0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma globulin. GAMMAKED contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. The distribution of IgG subclasses is similar to that found in normal serum. 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. [20] 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. [21] Residual caprylate concentrations in the final container are no more than 0.216 g/L (1.3 mg/mL). The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsm/kg solvent, which is close to physiological osmolality (285-295 mOsm/kg). The pH of GAMMAKED is 4.0-4.5. GAMMAKED contains no preservative and is latex-free.

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 1 (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 DNA viruses (e.g., herpes viruses); Reovirus type 3 (Reo-3) 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.
 Overall virus reduction was calculated only from steps that were mechanically 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 12: Log₁₀ Virus Reduction

Process Step	Log ₁₀ Virus Reduction					
	Enveloped Viruses		Non-enveloped Viruses			
	HIV	PRV	BVDV	Non-HAV	PPV	
Caprylate Precipitation/Depth Filtration	C/I ^a	C/I	2.7	≥3.5	≥3.6	4.0
Caprylate Incubation	≥4.5	≥4.6	≥4.5	NA ^b	NA	NA
Depth Filtration ^c	CAP ^c	CAP	CAP	≥4.3	≥2.0	3.3
Column Chromatography	≥3.0	≥3.3	4.0	≥4.0	≥1.4	4.2
Low pH Incubation	≥6.5	≥4.3	≥5.1	NA	NA	NA
Global Reduction	≥14.0	≥12.2	≥16.3	≥7.5	≥5.0	8.2

^a 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.

^b Not Applicable - This step has no effect on non-enveloped viruses.

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

Some mechanistic overlap occurs between depth filtration and other steps. Therefore, Talcres Biotherapeutics, Inc. has chosen to exclude this step from the global virus reduction calculations.

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 GJD agents. [22-26]

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 logs). 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
 Treatment of Primary Humoral Immunodeficiency

GAMMAKED supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viral, parasitic, mycoplasma agents, and their toxins. The mechanism of action in PI has not been fully elucidated.

Treatment of Chronic Inflammatory Demyelinating Polyneuropathy
 The precise mechanism of action in CIDP has not been fully elucidated.

12.2 Pharmacodynamics
 Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of GAMMAKED is IgG (≈98%) with a sub-class distribution of IgG1, IgG2, IgG3 and IgG4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

12.3 Pharmacokinetics
 Intravenous Administration:

Two randomized pharmacokinetic crossover trials were carried out with GAMMAKED in 38 subjects with Primary Humoral Immunodeficiencies given 3 infusions 3 or 4 weeks apart of test product at a dose of 100-500 mg/kg body weight per infusion. One trial compared the pharmacokinetic characteristics of GAMMAKED to GAMMUNE N, 10% and the other trial compared the pharmacokinetics of GAMMAKED (10% strength) with a 5% concentration of this product. The ratio of the geometric least square means for dose-normalized IgG peak levels of GAMMAKED and GAMMUNE N, 10% was 0.996. The corresponding value for the dose-normalized area under the curve (AUC) of IgG levels was 0.990. The results of both PK parameters were within the pre-established limits of 0.80 and 1.25. Similar results were obtained in the comparison of GAMMAKED 10% to a 5% concentration of GAMMAKED.

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

Table 13: PK Parameters of GAMMAKED™ and GAMMUNE® N, 10%

	GAMMAKED™			GAMMUNE® N, 10%				
	N	Mean	SD	Median	N	Mean	SD	Median
C _{max} (mg/mL)	17	19.04	3.06	19.71	17	19.31	4.17	19.30
C _{max-norm} (mg/mL)	17	0.047	0.007	0.046	17	0.047	0.008	0.047
AUC(0-72h) ^a (mg*hr/mL)	17	6746.48	1348.13	6949.47	17	6854.17	1425.08	7119.86
AUC(0-168h) ^a (kg*hr/mL)	17	16.51	1.83	16.95	17	16.69	2.04	16.99
T _{1/2β} (days)	16	35.74	8.69	33.09	16	34.27	9.28	31.88

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

^b Only 15 subjects were valid for the analysis of T_{1/2β}.
 The two pharmacokinetic trials with GAMMAKED show the IgG concentration/time curve follows a biphasic slope with a distribution phase of about 5 days characterized by a fall in serum IgG levels followed by a distribution phase of about 65-75% of the peak levels achieved immediately post-infusion. This phase is followed by the elimination phase with a half-life of approximately 35 days. IgG trough levels were measured over nine months in the therapeutic equivalence

trial. Mean trough levels were 7.8 ± 1.9 mg/mL for the GAMMAKED treatment group and 8.2 ± 2.0 mg/mL for the GAMMUNE N, 10% control group.

Subcutaneous Administration

Treatment of Primary Humoral Immunodeficiency by the Subcutaneous (SC) Route
 In a single sequence, open-label, crossover trial, the pharmacokinetics, safety, and tolerability of SC administered GAMMAKED in subjects with PI were evaluated. A total of 32 and 26 subjects received GAMMAKED as IV or SC for PK study, respectively. 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. The PK endpoint parameter (AUC of total plasma IgG) following IV and SC administration is summarized below in Table 14. The lower bound of the 90% confidence interval for the geometric mean ratio of AUC (SC vs. IV) was 0.861, therefore, meeting the pre-specified non-inferiority margin between the two modes of administration.

Table 14: Summary of PK Endpoint of AUC

Route of Administration	Statistics	AUC _{0-72h} (mg*hr/mL)	AUC _{0-168h} (mg*hr/mL)	Adj. AUC _{0-168h} (mg*hr/mL)
IV (n = 32)	Mean	7640	NA	NA
	%CV	15.9	NA	NA
	Range	5616-10400	NA	NA
SC (n = 26)	Mean	1947	6858	NA
	%CV	NA	20.4	18.1
	Range	1300-2758	5169-10364	NA

CV, coefficient of variation; NA, not applicable

¹ Adj. AUC_{0-168h}: Adjusted steady-state area under the concentration vs. time curve following SC administration based on IV dosing schedule, calculated as AUC_{0-168h} multiplied by 3 or 4 for subjects on every-3-week or every-4-week IV dosing schedule, respectively.

The mean trough concentration (mean C_{100h}) of total plasma IgG following IV and SC administration are presented in Table 15.

Table 15: Mean Plasma Trough Concentrations of Total IgG (mg/mL) in Plasma

	IV		SC	
	Mean	SD	Mean	SD
n	32	28	26	28
Mean (mg/mL)	9.58	11.4	7.82	11.4
%CV	22.3	20.4	20.4	20.4
Range	6.66-14.0	8.10-16.2	6.66-14.0	8.10-16.2