gammaked™

immune globulin injection (human), 10%
caprylate/chromatography purified

- 10% IG LIQUID SOLUTION, READY TO INFUSE
- SUCROSE-FREE
- 3-YEAR REFRIGERATED SHELF LIFE

INDICATED FOR THE TREATMENT OF:

CIDP chronic inflammatory demyelinating polyneuropathy in adults*

PI primary humoral immunodeficiency in patients 2 years of age and older†

ITP idiopathic thrombocytopenic purpura in adults and children‡

* to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse
† including but not limited to congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies
‡ to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery

IMPORTANT SAFETY INFORMATION

Boxed 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 vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known 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. 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.**

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KEDRION BIOPHARMA

THE ICE STUDY (IGIV-C CIDP EFFICACY)

THE ICE STUDY established the long-term efficacy of GAMMAKED for the treatment of CIDP[1,2]

It included 2 separately randomized periods designed to determine whether[1]:

1. GAMMAKED could be more effective than placebo in the treatment of CIDP (assessed in the initial 24-week Efficacy Period)
2. Long-term administration of GAMMAKED could maintain long-term benefit, such as lower probability of relapse (assessed in the Randomized Withdrawal Period, or Extension Phase, from weeks 24-48)

PATIENTS IN THE TREATMENT GROUP RECEIVED[2]:

> Loading dose of 2 g/kg GAMMAKED administered over 2-4 days

> Maintenance dose of 1 g/kg GAMMAKED every 3 weeks for up to 24 weeks

> Patients were evaluated using INCAT* disability scores at day 16 and at 3-week intervals thereafter

24-WEEK EFFICACY PERIOD + 24-WEEK EXTENSION PHASE
=
48-WEEK STUDY

***The Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score[1]**

> Validated, 10-point assessment used to evaluate disability in neuropathy research

> Patients evaluated on their ability to walk (scale of 0 to 5) and to perform certain arm functions (scale of 0 to 5)

> Overall 10-point INCAT disability score is the sum of arm and leg scores

GAMMAKED IS ADMINISTERED ONLY INTRAVENOUSLY FOR PATIENTS WITH CIDP[1]

DOSE	INITIAL INFUSION RATE	MAINTENANCE INFUSION RATE (IF TOLERATED)
Loading dose: 2 g/kg Maintenance dose: 1 g/kg	2 mg/kg/min (0.02 mL/kg/min)	8 mg/kg/min (0.08 mL/kg/min) Every 3 weeks

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

CIDP

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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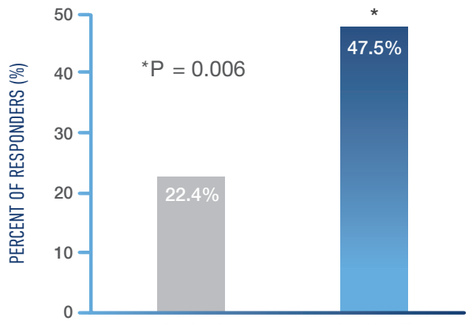
1 GAMMAKED improved physical functioning in CIDP

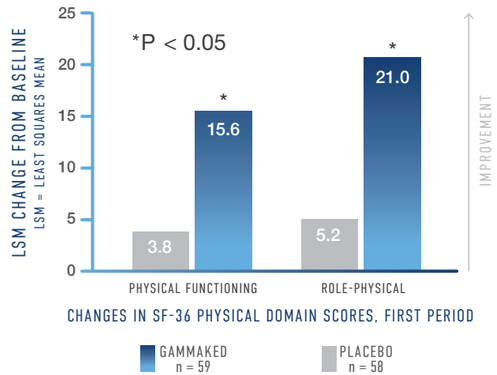
EFFICACY PERIOD (WEEKS 0-24)

For patients receiving GAMMAKED in the ICE Study:

A. INCAT disability scores maintained significant improvement through week 24[1†]



B. Significant improvement observed in physical domain scores[3‡]



[1]Responders defined as patients who maintained an improvement of ≥ 1 point in adjusted INCAT disability score through week 24.

[3]Participants were assessed using the SF-36 health survey. Domain scores were recorded at screening and at the end of each period.
> Physical functioning (includes ability to walk or climb stairs)[4]
> Role-physical (activities of daily living, including work)[4]

IMPORTANT SAFETY INFORMATION

> GAMMAKED is contraindicated in patients who have had an anaphylactic or severe systemic reaction to human immunoglobulin. It is also contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.

> Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including GAMMAKED.

> Aseptic Meningitis Syndrome (AMS) may occur infrequently, especially with high doses or rapid infusion.

> Hemolysis, either intravascular or due to enhanced red blood cell (RBC) sequestration, can develop subsequent to GAMMAKED treatment. 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.

> Noncardiogenic pulmonary edema may occur in patients following treatment with IGIV products, including GAMMAKED. Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).

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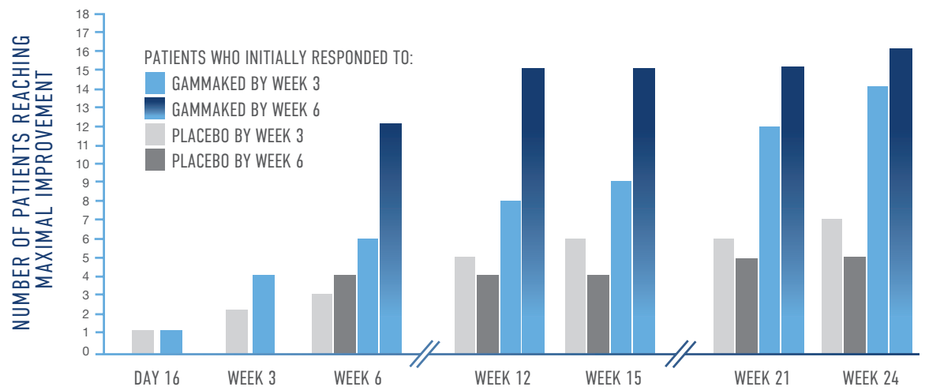
THE ICE STUDY (CONTINUED)

1 Continued improvement seen over the full 24 weeks[5]

EFFICACY PERIOD (WEEKS 0-24)

> Among CIDP patients who responded* to GAMMAKED
- 47% initially responded by week 3
- 53% initially responded by week 6

CUMULATIVE NUMBER OF RESPONDERS REACHING MAXIMUM IMPROVEMENT† IN INCAT DISABILITY SCORES



> The number of patients reaching their maximal improvement continued to increase for the full duration of GAMMAKED therapy (24 weeks)

> Discontinuing GAMMAKED treatment before maximal improvement is achieved may deprive patients the full therapeutic benefit, such as the abilities to walk unaided or dress the upper part of the body[6]

* Responders were defined as patients who maintained an improvement of ≥ 1 point in adjusted INCAT disability score through week 24
† An individual patient's maximal INCAT disability score over the course of the ICE Study

IMPORTANT SAFETY INFORMATION

> 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.

> GAMMAKED is made from human plasma. Because this product is made from human plasma, 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.

> GAMMAKED is not approved for subcutaneous use in patients with ITP. Due to the potential risk of hematoma formation, GAMMAKED should not be administered subcutaneously in patients with ITP.

> 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.

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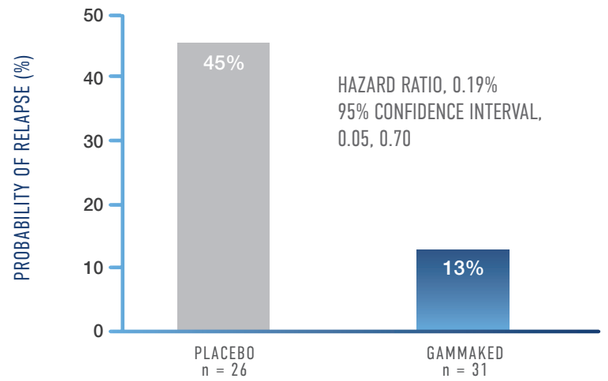
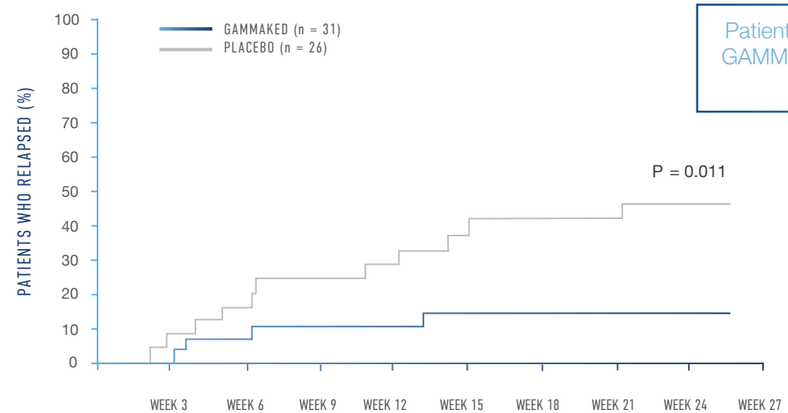
2 Long-term GAMMAKED administration can lower probability of relapse in CIDP[1]

EXTENSION PHASE (WEEKS 24-48)



HAZARD RATIO, 0.19%
95% CONFIDENCE INTERVAL,
0.05, 0.70

Withdrawal of therapy (re-randomization to placebo) increased risk of relapse[1]



Patients who continued to receive GAMMAKED experienced a longer time to relapse[1]

GAMMAKED is indicated for maintenance therapy to prevent CIDP relapse

See Full Prescribing Information for complete CIDP indication.

In CIDP clinical studies, the most common adverse reactions with GAMMAKED (≥5% of subjects) were headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

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PI

PRIMARY HUMORAL IMMUNODEFICIENCY

PROVEN TO PREVENT INFECTIONS IN PATIENTS WITH PI[7]

> As demonstrated in a 9 month study
> GAMMAKED is indicated for the treatment of PI in patients 2 years of age and older[1]
> This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies[1]

GAMMAKED CAN BE ADMINISTERED SUBCUTANEOUSLY (SC) FOR ADULT AND PEDIATRIC PATIENTS WITH PI[1]

ROUTE OF ADMINISTRATION	INITIAL DOSE	INITIAL INFUSION RATE	MAINTENANCE INFUSION RATE (IF TOLERATED)
Intravenous (IV)	300-600 mg/kg (may be adjusted over time to achieve desired trough levels and clinical responses)	1 mg/kg/min	8 mg/kg/min Every 3-4 weeks
Subcutaneous (SC)	1.37 x current IV dose in grams/ IV dose interval in weeks (should be individualized based on clinical response and serum IgG trough levels)	**Adult:*** 20 mL/hr/site **Pediatric:*** 10 mL/hr/site (< 25 kg) 15 mL/hr/site (≥ 25 kg)	**Adult:*** 20 mL/hr/site **Pediatric:*** 10 mL/hr/site (< 25 kg) 15 mL/hr/site (≥ 25 kg) Weekly

*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.

DO NOT ADMINISTER SUBCUTANEOUSLY FOR CIDP or ITP PATIENTS

ITP

IDIOPATHIC THROMBOCYTOPENIC PURPURA

PROVEN TO RAISE PLATELET COUNTS IN PATIENTS WITH ITP[8]

> GAMMAKED is indicated for the treatment of adults and children with ITP to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery[1]

GAMMAKED IS ADMINISTERED ONLY INTRAVENOUSLY FOR PATIENTS WITH ITP

DOSE	INITIAL INFUSION RATE	MAINTENANCE INFUSION RATE (IF TOLERATED)
2 g/kg	1 mg/kg/min (0.01 mL/kg/min)	8 mg/kg/min (0.08 mL/kg/min)

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IMPORTANT SAFETY INFORMATION

Boxed 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 vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known 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. 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.**

> GAMMAKED is contraindicated in patients who have had an anaphylactic or severe systemic reaction to human immunoglobulin. It is also contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.

> Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including GAMMAKED.

> Aseptic Meningitis Syndrome (AMS) may occur infrequently, especially with high doses or rapid infusion.

> Hemolysis, either intravascular or due to enhanced red blood cell (RBC) sequestration, can develop subsequent to GAMMAKED treatment. 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.

> Noncardiogenic pulmonary edema may occur in patients following treatment with IGIV products, including GAMMAKED. Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).

> 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.

> GAMMAKED is made from human plasma. Because this product is made from human plasma, 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.

> GAMMAKED is not approved for subcutaneous use in patients with ITP. Due to the potential risk of hematoma formation, GAMMAKED should not be administered subcutaneously in patients with ITP.

> 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.

> In clinical studies, the most common adverse reactions with GAMMAKED (≥5% of subjects) were: (in PI intravenous) cough increased, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis; (in PI 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; (in ITP) headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain, and dyspepsia; (in CIDP) headache, pyrexia, hypertension, chills, rash, nausea, arthralgia, and asthenia.

Please see accompanying Full Prescribing Information, located in the pocket, for complete prescribing details including Boxed Warning, contraindications and dosing and administration information.

STORAGE & HANDLING[1]

> Ready-to-infuse, 10% IG solution
> Built-in hanger on 5, 10, and 20 g vials
> 3-year refrigerated shelf life; up to 6-month room temperature storage (within total shelf life)*
> No components of vial made with natural rubber latex
> 5 color-coded package sizes with barcoding
> Peel-off labels to help simplify recordkeeping

*Up to 6 months at any time during 36-month shelf life, after which the product should be used immediately or discarded

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GAMMAKED PROPERTIES[1]

> Sucrose-free
> Glycine stabilized
> Near physiologic osmolality
> pH of solution: 4.0-4.5
> Trace amounts of IgA (average 46 mcg/mL)

APPROVED IN 5 SIZES:

IMPORTANT SAFETY INFORMATION

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References: 1. GAMMAKED [prescribing information]. Fort Lee, NJ: Kedrion Biopharma Inc.; 2018. **2.** Hughes RAC, Donofrio P, Bril V, et al, on behalf of the ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study); a randomised placebo-controlled trial. *Lancet Neurol.* 2008;7:136-44. **3.** Merkies ISJ, Bril V, Dalakas MC, et al. Health-related quality-of-life improvements in CIDP with immune globulin IV 10%: The ICE Study. *Neurology.* 2009;72:1337-44. **4.** McHorney CA, Ware JE Jr., Lu JFR, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care.* 1994;32:40-66. **5.** Latov N, Deng C, Dalakas MC, et al, for the IGIV-C CIDP Efficacy (ICE) Study Group. Timing and course of clinical response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Arch Neurol.* 2010;67(7):802-807. **6.** Merkies ISJ, Schmitz PIM, van der Meche FGA, et al, for the INCAT group. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies. *J Neurol Neurosurg Psychiatry.* 2002;72:596-601. **7.** Roifman CM, Schroeder H, Berger M, et al, and the IGIV-C in PID Study Group. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: a randomized double-blind trial. *Int Immunopharmacol.* 2003;3:1325-33. **8.** Bussel JB, Eldor A, Kelton JG, et al. IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action and impact on quality of life. *Thromb Haemost.* 2004;91:771–8.

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