# Intravenous Immune Globulin side-by-side comparison

(with a Subcutaneous Immune Globulin product comparison)

September 2021

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# Evidence Summary and Conclusions

### Introduction

Currently there are 11 intravenous immune globulin (IVIG) products approved by the U.S. Food and Drug Administration (FDA): Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gamunex-C, Gammaplex, Octagam, Panzyga, and Privigen. The products vary in content, composition, and properties. These products account for 7 FDA-approved indications, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic lymphocytic leukemia (CLL), dermatomyositis (DM), immune thrombocytopenic purpura (ITP), Kawasaki syndrome (KS), multifocal motor neuropathy (MMN), and primary immunodeficiency disease (PI); however, not all products are approved for each indication.[a-n] Additionally, there are numerous off-label uses which have been published in consensus statements/guidelines to promote evidence-based use of IVIG off-label.[o] **A comparison of subcutaneous immune globulin (SCIG) products can be found in Appendix 1.**

### Guidelines

The American Academy of Allergy, Asthma, and Immunology (AAAAI) guidelines review the evidence for the use of IVIG in a variety of disease states including primary immunodeficiencies, secondary immunodeficiencies, autoimmune diseases, atopic diseases, infectious and infection-related diseases, neurologic disorders, and other miscellaneous disease states. The guidelines recommend careful consideration of IVIG administration and its indications due to the potential risks associated with its use and the inherent scarcity of human immune globulins.[o]

### Formulation differences

*Viral inactivation*

All IVIG products have the potential to transmit blood-borne pathogens; therefore, all manufacturers employ several mechanisms to reduce or eliminate viral load. Only the viral inactivation processes used for Flebogamma DIF, Gamunex-C, Gammaked, Panzyga, and Privigen are validated for removal of pathogenic prions that may cause transmissible spongiform encephalopathies (TSE) disease in humans.

*Sodium content*

Increasing sodium content may be associated with an increased incidence of thrombotic and other adverse events. Sodium content should be considered in neonatal and geriatric patients and patients presenting with cardiac conditions, renal insufficiency, and/or thromboembolic disorders.[r] Most of the ready-to-use liquids contain only trace amounts of sodium while the sodium content of lyophilized products is doubled when the concentration is doubled.[a-n]

*Sugar content*

Gammagard S/D and Octagam contain sugars as stabilizers to minimize the formation of IgG aggregates.[f,l] According to the CDC, over 90% of the reported cases of IVIG-associated renal failure have occurred in sucrose-containing IVIG products while 8% occurred in glucose/maltose-containing IVIG products.[p] Due to the potential for renal failure, carbohydrate-stabilized IVIG products should be avoided in patients with renal insufficiency. Many of the newer products are stabilized with amino acids and may be better choices, if available, for use in patients with renal insufficiency. In patients with diabetes, the stabilizer should also be considered in product choice. Products stabilized with glucose will increase blood glucose levels whereas products stabilized with sucrose, maltose, or amino acids have no effect on glucose levels.[q]

*Osmolarity/osmolality*

Osmolarity/osmolality is related to the sugar and sodium content of the product. Hyperosmolar products may be more likely to cause thrombotic and renal adverse events than products that are iso-osmolar. Generally, hyperosmolar products should be avoided in neonates, patients with pre-existing renal insufficiency, and in patients with a history of thromboembolic disorder. IVIG products formulated at more acidic pHs may increase the risk of phlebitis; however, for most patients, the acid load is rapidly neutralized by the blood's buffering system. Neonatal patients are the exception. In neonates, a product with an acidic pH can cause phlebitis in the peripheral veins.[r]

*IgA*

All IVIG products contain small amounts of IgA with the smallest amount in Gammagard S/D.[a-n] The maximum tolerable amount of IgA is unknown, but the presence of IgA is most likely only significant in patients with IgA deficiency.

*Convenience factors*

IVIG products have protein concentrations of 5% and 10%. Higher concentrations require less volume for a given dose and smaller volumes require shorter infusions time, which may reduce administration turnaround time.[a-n] Patients who may not tolerate increased infusion volumes include neonatal or geriatric patients, patients with cardiac conditions, pulmonary edema, renal insufficiency, or those at risk of thromboembolic events.[r] Additionally, IVIG products are formulated as either lyophilized/freeze-dried powders or ready-to-use liquids. Lyophilized/freeze-dried products must be reconstituted prior to use and have a limited window for administration following reconstitution. In the event a patient does not show up for an appointment, ready-to-use liquid products may help to avoid waste. Differences in storage requirements and shelf life between liquid products should be considered as convenience factors. Lastly, vial size may be an important consideration if there is a large pediatric population. Although the IVIG dose may be rounded to the nearest vial size, provided the rounded dose is within 10% of the original dose ordered, significant wastage may still occur if only larger vial sizes are available

**Dosing weight**

Dosing of IVIG can be achieved using actual body weight (ABW), ideal body weight (IBW), or adjusted body weight (AdjBW).[s] Various retrospective analyses have shown no difference in readmission rate, length of stay, infection rate, or IgG-level response amongst the three dosing weights.[t-x] Selection of the dosing weight based on patient-specific variables can decrease waste and improve cost savings, while maintaining clinical efficacy.[y,z] After administration, IVIG is present in the intravascular space and extracellular fluids. It is a polar molecule with a small volume of distribution and does not distribute into adipose tissue. Based on its pharmacokinetic properties, AdjBW dosing is appropriate for patients with BMI ≥30 kg/m$^2$ or if ABW greater than 20%-30% over IBW (dependent on institutional definition of obesity) as it is presumed extracellular fluid is increased in patients with increased adipose tissue.[x] Data on the appropriate dosing weight in obese patients is limited and differing pharmacokinetics amongst patient populations has been observed; therefore, dose adjustments should be made based on clinical outcomes.[aa,bb]

*Recommendations*: dependent of patient-specific variables

1) Use IBW
2) Use ABW (if ABW <IBW)
3) Use AdjBW (if BMI ≥30 kg/m$^2$ or if ABW greater than 20%-30% over IBW per institutional definition of obesity)

**Clinical efficacy**

The majority of IVIG products were evaluated in single-arm, open-label, non-randomized trials. Primary outcomes included platelet counts and acute serious bacterial infections. There is a paucity of head-to-head trials comparing one commercial product with another; therefore, it is unknown if differences in manufacturing processes play a role in clinical efficacy.

**Conclusions**

Patient-specific factors for selection of an IVIG product include tolerability, adverse effects, safety, and convenience of use. Health system-specific factors to consider when choosing between IVIG products include acquisition cost of the product, reimbursement, preparation cost, storage and shelf life, infusion time, adverse event profile, and product availability.

## IVIG side-by-side comparison

| Brand name | Asceniv | Bivigam | Flebogamma DIF | Gammagard Liquid | Gammagard S/D | Gammaked[a] Gamunex-C | Gammaplex | Octagam | Panzyga | Privigen |
|---|---|---|---|---|---|---|---|---|---|---|
| **Manufacturer** | ADMA Biologics | ADMA Biologics | Grifols | Takeda | Takeda | • Grifols for Kedrion<br>• Grifols | Bio Products Laboratory | Octapharma | Octapharma | CSL Behring |
| **Dosage form** | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Lyophilized | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid |
| **Concentration** | 10% | 10% | 5%, 10% | 10% | 5%[b], 10% | 10% | 5%, 10% | 5%, 10% | 10% | 10% |
| **FDA-approved indications (adult unless other specified)** | | | | | | | | | | |
| *CIDP* | -- | -- | -- | -- | -- | **X** | -- | -- | **X** | **X** |
| *CLL* | -- | -- | -- | -- | **X** | -- | -- | -- | -- | -- |
| *DM* | -- | -- | -- | -- | -- | -- | -- | **X** (10%) | -- | -- |
| *ITP* | -- | -- | **X** - Chronic in ≥2 y (10%) | -- | **X** | **X** - Pediatrics and adults | **X** - Chronic (5% evaluated in pediatric patients, 10%) | **X** - Chronic (10%) | **X** - Chronic | **X** - Chronic ≥15 y |
| *KS* | -- | -- | -- | -- | **X** - Pediatrics | -- | -- | -- | -- | -- |
| *MMN* | -- | -- | -- | **X** | -- | -- | -- | -- | -- | -- |
| *PI* | **X** - ≥12 y | **X** (evaluated in pediatrics ≥6 y) | **X** - ≥2 y (5%); adults (10%) | **X** - ≥2 y | **X** - ≥2 y | **X** - ≥2 y | **X** - ≥2 y (5%, 10%) | **X** (5%, evaluated in pediatrics ≥6 y) | **X** - ≥2 y | **X** – (evaluated in pediatrics ≥3 y) |
| **Plasma source** | FDA-approved plasmapheresis centers | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| **Specific viral inactivation/ removal process** | • Cold ethanol fractionation<br>• SD<br>• Nanofiltration (35 nm) | • Cold ethanol fractionation<br>• SD<br>• Nanofiltration (35 nm) | • Pasteurization (60°C, 10 h)<br>• SD<br>• Nanofiltration (20 nm)<br>• Fraction I precipitation<br>• Fraction II + III incubation<br>• PEG precipitation<br>• Acid treatment | • SD<br>• Nanofiltration (35 nm)<br>• Low pH incubation | • Cold ethanol fractionation<br>• SD<br>• Ion-exchange chromatography | • Caprylate precipitation/ depth filtration<br>• Caprylate incubation<br>• Column chromatography<br>• Depth filtration<br>• Nanofiltration<br>• Low pH incubation | • SD<br>• Nanofiltration (20 nm)<br>• Low pH incubation | • Cold ethanol fractionation<br>• SD<br>• Low pH treatment | • SD<br>• Ion-exchange chromatography<br>• Nanofiltration (20 nm) | • Low pH incubation<br>• Depth filtration<br>• Nanofiltration (20 nm) |
| **Validated TSE removal steps** | No | No | Yes | No | No | Yes | No | No | Yes | Yes |
| **Pharmacology** | Intravenous immune globulins are sterile preparations of concentrated antibodies (immune globulins) recovered from pooled human plasma of healthy donors. These preparations provide replacement therapy for patients with immune deficiencies, as well as treatment for a variety of immunologically mediated or idiopathic diseases and syndromes. | | | | | | | | | |
| **Pharmacokinetics/stability** | | | | | | | | | | |
| *Half-life (d)* | • 3-wk dosing: 28.5 ± 4.4<br>• 4-wk dosing: 39.7 ± 11.6 | • 3-wk dosing: 19.6 ± 4.1<br>• 4-wk dosing: 33.5 ± 10.7 | 3-wk dosing:<br>• 30 ± 11 (5%)<br>• 34 ± 10 (10%)<br>4-wk dosing:<br>• 32 ± 7 (5%)<br>• 37 ± 13 (10%) | 35 (median) | 37.7 ± 15 | 35[c] | 4-wk dosing[c]<br>• 41 ± 14 (5%)<br>• 34.8 (10%) | • 40.7 ± 17 (5%)<br>• 36 - 40 (10%)[c] | • 3-wk dosing: 32.4 ± 12.4<br>• 4-wk dosing: 45.1 ± 20.8 | • 3-wk dosing: 27.6 ± 5.9<br>• 4-wk dosing: 45.4 ± 18.5 |
| *Storage* | 2 - 8°C<br>• Do not freeze or heat | 2 - 8°C<br>• Do not freeze or heat | 2 - 25°C<br>• Do not freeze<br>• Protect from light | 2 - 8°C or ≤25°C<br>• Do not freeze | ≤25°C<br>• Do not freeze | 2 - 8°C or ≤25°C<br>• Do not freeze | 2 - 25°C<br>• Do not freeze<br>• Protect from light | 2 - 25°C (5%);<br>2 - 8°C or ≤25°C (10%)<br>• Do not freeze | 2 - 8°C or ≤25°C<br>• Do not freeze | ≤ 25°C<br>• Do not freeze<br>• Protect from light |

| Brand name | Asceniv | Bivigam | Flebogamma DIF | Gammagard Liquid | Gammagard S/D | Gammaked[a] Gamunex-C | Gammaplex | Octagam | Panzyga | Privigen |
|---|---|---|---|---|---|---|---|---|---|---|
| *Shelf-life (mo)* | 24, consistent with the expiration date on the label | 24, consistent with the expiration date on the label | 24 at room temperature | • 36 if stored under refrigeration<br>• 24 if stored at room temperature | 24 | • 36 from date of manufacture if stored under refrigeration<br>• Product may be stored at temperatures not to exceed 25°C for up to 6 mo anytime during the 36 mo shelf life | 36 | • 24 from date of manufacture if stored at 2 - 25 °C (5%) or 2 - 8°C (10%)<br>• Within the first 12 mo of shelf-life, may store up to 9 mo at ≤25° C (10%) | • 36 from date of manufacture if stored under refrigeration.<br>• Product may be stored at temperatures not to exceed ≤25° C for up to 12 mo during its shelf life | 36 |
| **Contraindications** | | | | | | | | | | |
| *Anaphylaxis/ severe systemic reactions to human IG or other components* | X | X | X | X | X | X | X | X | X | X |
| *IgA deficiency with antibodies to IgA and a history of hypersensitivity* | X | X | X | X | -- | X | X | X | X | X |
| *Other* | -- | -- | -- | -- | -- | -- | Hereditary intolerance to fructose<br>Pediatrics for whom sucrose or fructose tolerance is not established (5%) | Hypersensitivity to corn | -- | Hyperprolinemia |
| **Boxed warning** | Thrombosis may occur with IVIG products. 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. IVIG products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. In patients predisposed to acute renal failure, administer at the minimum concentration available and the minimum rate of infusion practicable. Renal effects are more common with high sucrose content and high osmolality. Make sure patients are not volume depleted prior to administration. | | | | | | | | | |
| **Warnings and precautions** | May carry a risk of transmitting infectious agents due to human plasma origin, including (theoretically) Creutzfeldt-Jakob disease agent. May be associated with hemolytic anemia, thromboembolic events, transfusion-related acute lung injury, aseptic meningitis syndrome, hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia. IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Periodic monitoring of renal function and urine output is important in patients at risk for acute renal failure. | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | -- | -- | Contains sorbitol, which may be a risk factor for those with hereditary fructose intolerance | -- | -- | Due to risk of hematoma formation, do not administer subcutaneously in ITP | Consider risks and benefits before administering high dose regimen in patients with chronic ITP | Falsely elevated glucose readings may occur after infusion with some glucometers and test strips | -- | Consider risks and benefits before administering high- dose regimen for at risk patients |
| **Adverse reactions** | Adverse event profiles are often patient-specific. Brand, concentration, and rate of infusion may influence patient tolerability. Common side effects include hypotension, hypertension, and headache, which can be diminished by reducing infusion rate. Flu-like symptoms may occur several hours or days after infusion and can be managed with non-steroidal anti-inflammatory agents. Back- and leg-pain syndrome, and fever and shaking can be managed by stopping the infusion, administering methylprednisolone, diphenhydramine, and a sufficient dose of intravenous narcotic analgesics; once controlled, infusion may be restarted. Most patients develop tolerance, but if side effects become intolerable, another brand of IVIG may be administered. | | | | | | | | | |
| | Incidence ≥5%: Headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, and nausea | Incidence ≥5%: Headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increases, diarrhea, dizziness, and lethargy | **PI** (≥5%): 5% - Headache, pyrexia/ fever, pain, infusion site reactions, diarrhea, rigors, or chills, urticaria, infusion site inflammation 10% - Headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and extremity pain **ITP** (≥5%): Headache, pyrexia, nausea, chills, vomiting, body temperature increased, dizziness, back pain, hypotension, hypertension, heart rate increased and diarrhea | **PI** (≥5%): Headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur **MMN** (≥5%): Headache, chest discomfort, muscle spasms, muscular weakness, nausea, oropharyngeal pain, and pain in extremity | Incidence ≥5%: Headache, nausea, chills, fatigue, pyrexia, upper abdominal pain, diarrhea, back pain, infusion site pain, hyperhidrosis, and flushing | **PI** (≥5%): Increased cough, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis **ITP** (≥5%): Headache, ecchymosis, vomiting, fever, nausea, rash, abdominal pain, back pain, and dyspepsia **CIDP** (≥5%): Headache, fever, chills, hypertension, rash, nausea, arthralgia, and asthenia | **PI** (≥5%): 5% - Headache, pyrexia, nasal congestion and edema, fatigue, nausea, hypertension, rash, hypotension, infusion site reaction, vomiting, myalgia, chills, tachycardia, chest pain/discomfort, pain, dizziness, malaise, dysuria and dry skin. 10% - Headache, migraine, and pyrexia **Chronic ITP** (≥5%): Headache, vomiting, nausea, pyrexia, dehydration, and arthralgia | (≥5%): 5% - Headache and nausea (≥5%): 10% - Headache, fever, and increased heart rate | **PI** (>5%): Headache, nausea, fever, fatigue, and abdominal pain **CIDP** (>5%): headache, fever, dermatitis, blood pressure increased **ITP** (>5%): Headache, fever, nausea, vomiting, dizziness, and anemia | **PI** (≥5%): Headache, fatigue, nausea, chills, vomiting, pain, pyrexia, abdominal pain, diarrhea, cough, stomach discomfort, chest pain, joint swelling/effusion, ILI, pharyngolaryngeal pain, urticarial and dizziness **ITP** (≥5%): Headache, pyrexia, anemia, vomiting, nausea, hyperbilirubinemia, increased lactate dehydrogenase, (+) direct antiglobulin **CIDP** (≥5%): ILI, headache, asthenia, hypertension, nausea, pain in extremity, hemolysis, and leukopenia |
| **Administration – Consult individual prescribing information for specific dosing guidance** | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| *Route* | IV | IV | IV | IV (PI, MMN) Subcutaneous (PI) | IV | IV (PI, ITP, CIDP) Subcutaneous (PI) | IV | IV | IV | IV |
| *Initial infusion rate (IV only)* | 0.5 mg/kg/min for 15 min | 0.5 mg/kg/min for 10 min | • 0.5 mg/kg/min (5%)<br>• 1 mg/kg/min (10%) for 30 min | 0.8 mg/kg/min for 30 min | 0.5 mL/kg/h (5%, 10%) | • 1 mg/kg/min (PI, ITP)<br>• 2 mg/kg/min (CIDP) | 0.5 mg/kg/min (5%, 10%) for 15 min | • 0.5 mg/kg/min (5%) for 30 min<br>• 1 mg/kg/min (10%, ITP, DM) | 1 mg/kg/min for 30 min | 0.5 mg/kg/min |
| *Maximum infusion rate (IV only)* | 8 mg/kg/min | 6 mg/kg/min | • 5 mg/kg/min (5%)<br>• 8 mg/kg/min (10%) | • 8 mg/kg/min (PI)<br>• 9 mg/kg/min (MMN) | • 4 mL/kg/h (5%)<br>• 8 mL/kg/h (10%) | 8 mg/kg/min | • 4 mg/kg/min (5%)<br>• 8 mg/kg/min (10%) | • 3.33 mg/kg/min (5%)<br>• 12 mg/kg/min (10%, ITP)<br>• 4 mg/kg/min (10%, DM) | • 14 mg/kg/min (PI)<br>• 12 mg/kg/min (CIDP)<br>• 8 mg/kg/min (ITP) | • 4 mg/kg/min (ITP)<br>• 8 mg/kg/min (PI, CIDP) |
| *Infusion rate in renal disease* | Infuse at the minimum rate practical | | | | | | | | Do not exceed 3.3 mg/kg/min | Infuse at the minimum rate practical |
| *Reconstitution/ dilution* | Do not dilute | Do not dilute | Do not dilute | May be diluted with D5W | Reconstitute with sterile water supplied | May be diluted with D5W | Do not dilute | Do not dilute | Do not dilute | May be diluted with D5W |
| *Reconstitution time* | -- | -- | -- | -- | If warm, < 5 min<br>If cold, > 20 min | -- | -- | -- | -- | -- |
| *Filter* | No | No | No | Optional | Yes - 15 micron filter provided | No | No | Optional (0.2 – 200 micron) | Optional (0.2 – 200 micron) | No |
| *Line flush* | Not available | Not available | Not available | 0.9% NaCl | Not available | D5W or 0.9% NaCl | 0.9% NaCl[d] | D5W or 0.9% NaCl | D5W or 0.9% NaCl | D5W or 0.9% NaCl |
| **Content characteristics** | | | | | | | | | | |
| *IgG (%)* | ≥96 | ≥96 | ≥97 | ≥98 | >90 | ≥98 | • >95 (5%)<br>• ≥98 (10%) | ≥96 | ≥96 | ≥98 |
| *IgA (mcg/ml)* | ≤200 | ≤200 | • <50 (5%)<br>• <100 (10%) | 37 | <1 (5%)[e] | 46 | • <10 (5%)<br>• <20 (10%) | • <200 (5%)<br>• 106 (10%) | 100 | ≤25 |
| *Albumin* | ≤2%[c] | ≤2%[c] | • <2 mcg/mL (5%)[c]<br>• <5 mcg/mL (10%)[c] | Not available | 3 mg/mL (5%)[e] | <2 mcg/ml[c] | 0[c] | 0[c] | 0[c] | ≤2%[c] |

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|---|---|---|---|---|---|---|---|---|---|---|
| *PEG* | Not available | Not available | • ≤3 mg/mL (5%)<br>• ≤6 mg/mL (10%) | Not detectable[c] | 2 mg/mL (5%)[e] | 0[c] | 0[c] | 0[c] | 0[c] | Not available[c] |
| **Content characteristics (continued)** | | | | | | | | | | |
| *Stabilizer* | Glycine | Glycine | 5% sorbitol | Glycine | 20 mg/mL glucose (5%)[e] and 22.5 mg/mL glycine (5%)[e] | Glycine | Polysorbate 80, sorbitol, glycine (5%)<br>Polysorbate 80, glycine (10%) | Maltose | Glycine | Proline |
| *Sugar content* | None | None | None | None | 20 mg/mL glucose (5%)[e] | None | None | • 100 mg/mL (5%) maltose<br>• 90 mg/mL (10%) maltose | None | None |
| *Sodium content* | 0.100 - 0.140 M | 0.100 - 0.140 M | Trace (<3.2 mEq/L)[c] | None | 8.5 mg/ml (5%)[e] | Trace (<7 mEq/L)[c] | 30 - 50 mM (5%)[c]<br><30 mM (10%) | ≤30 mmol/L | Trace amounts | Trace amounts |
| *pH when reconstituted* | 4.0 - 4.6 | 4.0 - 4.6 | 5 - 6 | 4.6 - 5.1 | 6.8 ± 0.4 | 4.0 - 4.5 | 4.8 - 5.1 (5%)<br>4.9 - 5.3 (10%) | 5.1 - 6.0 (5%)<br>4.5 - 5.0 (10%) | 4.5 - 5.0 | 4.8 (4.6 - 5.0) |
| *Osmolality (mOsmol/kg)* | 370 - 510[c] | 370 - 510[c] | 240 - 370 | 240 - 300 | Osmolarity 636 mOsm/L (5%)[c]<br>1250 mOsm/L (10%)[c] | 258 | 420 - 500 (5%)<br>280 (10%) | 310 - 380 | 240 - 310 | 320 (240 - 440) |
| **Interactions** | May interfere with response to live viral vaccines; appropriately delay for 3 or more months from time of IVIG administration. Do not mix with other drugs - administer via separate infusion line. Due to the maltose component, use of Octagam is associated with falsely elevated glucose values in glucose meters that use the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) method for testing. Passive transfer of antibodies may confound serologic testing. | | | | | | | | | |
| **Latex-free** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Tamper-evident** | Yes (vial) | Yes (vial) | Yes (overseal)[c] | Yes (cap)[c] | Yes (cap)[c] | Yes (vial - shrink band) | Yes (cap) | Yes[c] | Yes[c] | Yes (vial) |
| **Vial size** | 5 g | 5 g, 10 g | • 5%: 0.5 g, 2.5 g, 5 g, 10 g, 20 g<br>• 10%: 5 g, 10 g, 20 g | 1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g | 5 g, 10 g | • Gamunex-C: 1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g<br>• Gammaked: 1 g, 2.5 g, 5 g, 10 g, 20 g | • 5%: 5 g, 10 g, 20 g<br>• 10%: 5 g, 10 g, 20 g | • 5%: 1 g, 2.5 g, 5 g, 10 g, 25 g<br>• 10%: 2 g, 5 g, 10 g, 20 g, 30 g | 1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g | 5 g, 10 g, 20 g, 40 g |

| Brand name | Asceniv | Bivigam | Flebogamma DIF | Gammagard Liquid | Gammagard S/D | Gammaked[a] Gamunex-C | Gammaplex | Octagam | Panzyga | Privigen |
|---|---|---|---|---|---|---|---|---|---|---|
| **Enhancements** | Peel-off label (lot number, expiration date) | Peel-off label (lot number, expiration date) | • Laser etched vial<br>• Integral suspension band<br>• Peel-off label (lot number) | Peel-off label (lot number, expiration date) | • Peel-off label (lot number, expiration date)<br>• Diluent, transfer device, administration set that contains an integral airway and a filter | • Laser etched vial[c]<br>• Integrated hangers for 4 larger vial sizes<br>• Peel-off label (lot number) | Peel-off label (product name, batch number, expiration date) | Peel-off label (lot number, expiration date) | Peel-off label (lot number, expiration date)[c] | • Integral suspension band<br>• Peel-off label (lot number, expiration date) |

[a] Grifols manufactures Gammaked for Kedrion. Gamunex and Gammaked are the same product.

[b] A 10% solution can be prepared by using half the volume of diluent supplied.

[c] Siegl J. Immune Globulins: Therapeutic, pharmaceutical, cost and administration considerations. Pharmacy Practice News website. https://www.pharmacypracticenews.com/Review-Articles/Article/02-18/Immune-Globulins-Therapeutic-Pharmaceutical-Cost-and-Administration-Considerations/46805. Published February 9, 2021. Accessed June 5, 2021.

[d] Person communication, Jamie Urbanik, BPL, July 2017.

[e] For the 10% concentration, amount is doubled.

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| **Studies** | **Asceniv**<br>• *J Clin Immunol*. 2016 Aug;36(6): 590-9.[cc] In a multicenter, single-arm, prospective, open-label, non-randomized, phase 3 trial, patients with PI were administered Asceniv (n = 59) at doses of 300  800 mg/kg every 3 or 4 weeks for 12 months. Doses were adjusted to maintain trough IgG concentrations > 500 mg/dL or at the investigator's discretion. Inclusion criteria consisted of patients 2 to 75 years of age with confirmed PI who received IVIG infusions every 3 or 4 weeks at a stable dose (mean dose not changed by > 50%) for ≥ 3 months. The primary outcome was demonstration of a serious bacterial infection rate < 1.0 per person-year during the 12-month treatment with Asceniv. At 12 months, no serious bacterial infections were observed in the patient cohort, yielding a rate of infection < 1.0 per person-year. There were 3.436 infections of any kind per patient per year (one-sided 95% CI, upper bound 3.869). Days lost from work, school, or daycare was 1.66 days per patient per year. Unscheduled emergency room or medical visits due to infection was 0.966 visits per patient per year. There were 0.018 hospitalizations per patient per year due to infection. No serious adverse events were attributed to Asceniv over the course of the trial.<br>**Bivigam**<br>• *J Clin Immunol.* 2012;32(4):663-9.[dd] In a 12-month, single-arm trial, 58 patients with PI, a history of hypogammaglobulinemia, or deficient antibody production prior to IgG replacement therapy received Bivigam 300 to 800 mg/kg every 3 to 4 weeks. In the ITT data set, 2 SBIs occurred for an incidence rate of 0.035 SBI/patient/year with an upper 99% confidence interval limit of ≤ 0.136 SBI/patient/year. A total of 27.7% of infusions were associated with one or more adverse events (upper bound of 95% confidence interval, ≤ 30.6%). Adverse events occurring at an incident rate of greater than 20% were headache, sinusitis, fatigue, upper respiratory tract infection, cough, pharyngolaryngeal pain, and diarrhea.<br>**Flebogamma**<br>• *J Clin Immunol*. 2004;24(4):389-396.[ee] Flebogamma 5% (original formulation) was administered at 7 clinical sites to 51 subjects with PI at a dose of 300-600 mg/kg every 21 to 28 days for 12 months. The calculated SBIs rate for the ITT population was 0.061/subject/year (upper bound 99% CI of 0.183). Treatment-related adverse events occurring at an incidence of 10% or greater included pyrexia and headache.<br>• *Transfus Med*. 2009;19(5):260-8.[ff] Twenty adult subjects with chronic ITP were administered Flebogamma 5% DIF at a dose of 0.4 grams/kg/day for 5 days. In the ITT population, 14/20 (70%) of patients experienced a response, defined as a platelet count greater than or equal to 50 x 109/L. The median time to platelet response was less than or equal to 2.5 days. Common adverse events were petechiae, headache, pyrexia, and nasal bleeding.<br>• *J Clin Immunol*. 2010;30(2):321-9.[gg] In patients with well-defined PI (n=46), Flebogamma 10% DIF was administered every 3 to 4 weeks for a minimum of 12 months. In the ITT population, there was a single episode of pneumonia. The overall rate of aSBIs was 0.025 aSBIs/subject/year (98% CI, 0.001 to 0.133). Treatment-related adverse events occurring at an incidence of 10% or greater included headache, rigors, fever, tachycardia, hypotension, back pain, and myalgia.<br>• *J Clin Immunol.* 2007;27(6):628-633.[hh] Subjects (n = 46) with PI received Flebogamma 5% DIF every 3 to 4 weeks for 12 months in a multi-center, single-arm trial. During the study period, one patient experienced an aSBI resulting in a calculated rate of 0.021 SBIs/subject/year (upper bound of 98% CI was 0.112). The most common infusion-related adverse events were headache, fever, injection site reactions, diarrhea, and rigors.<br>• *Immunotherapy*. 2016;8(12):1371-1381.[ii] Seventy-six ITP patients in 2 multicenter studies (18 in Trial A (adults) and 58 in Trial B (adults/children)) were treated with 2 g/kg Flebogamma 10% (over 2-5 days) and were followed for 1 to 3 months. The response rate (platelet count ≥50 × 109/L) was 72.2% (95% CI, 50.2 to 88.4%) and 76.1% (95% CI, 63.5 to 86.0%) in Trials A and B, respectively, for the adult mITT population. The response rate in children (n=12) was 100%. Most patients experienced improvement in bleeding diathesis (83.3% Trial A; 88.9% Trial B). The most common adverse events were headache, pyrexia, nausea, chills, contusion, hypotension, and vomiting.<br>• *J Clin Immunol.* 2016;36(6):583-9.[jj] Twenty-four subjects (ages 2 – 16) with well-defined PI were administered Flebogamma 5% DIF at a dose of 300 to 800 mg/kg every 21 to 28 days for 12 months to evaluate efficacy, safety, and pharmacokinetics. The observed SBI rate was 0.051/subject/year (upper bound 99 % CI of 0.0526). The most commonly (≥5 %) reported treatment-related adverse events were headache (10 subjects, 41.7 %), pyrexia (7 subjects, 29.2 %), hypotension and tachycardia (6 subjects each, 25.0 %), and diastolic hypotension (5 subjects, 20.8 %).<br>• *Pharmacol Res Perspect*. 2017;5(5):e00345.[kk] The safety and efficacy of Flebogamma 5% and 10% DIF were compared in 69 patients (34 received 10% and 35 received 5%). Twenty-four infusions (18.5%; 95% CI, 11.8 to 25.1) with the 10% product and 3 (2.2%; 95% CI: -0.3 to 4.7) with the 5% product were associated with potentially treatment-related adverse events (P <.0001). The profile of adverse events occurring with infusion of 10% and 5% products were comparable. The most frequent treatment-related AEs were headache (n = 17) and pyrexia (n = 6).<br>**Gammagard**<br>• *J Clin Immunol*. 2006;26:388-395.[ll] In a single-arm trial, 61 patients diagnosed with PI disease that had received IVIG for at least 4 months pre-study, were administered Gammagard liquid every 3 to 4 weeks for a minimum of 12 months. In the ITT population, no aSBIs occurred.  The estimated 95% CI for the occurrence of aSBIs was 0 to 0.060 aSBIs/subject/year. Headache, fever, and fatigue were the most commonly reported adverse events. |

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| **Studies** | **Gamunex**<br>• *Int Immunopharmacol*. 2003;3(9):1325-1333.[mm] Investigators compared Gamunex with a solvent/detergent-treated product (Gamimune N) in patients with PI (n=172) in this randomized, double-blind study. After 9 months of therapy, the annual validated infection rates were 0.18 and 0.43, respectively (P = 0.023). Validated infections occurred in 9 and 17 patients, respectively (P = 0.06).<br>• *Thromb Haemost.* 2004;91(4):771-8.[nn] Investigators compared Gamunex with a solvent/detergent-treated product (Gamimune N) in patients with ITP (n=97) in this prospective, multicenter, randomized, double-blind, non-inferiority trial. Platelet counts increased above 50 x$10^9$/L within 7 days of dosing in 90% and 83%, respectively; counts were maintained above 50 x$10^9$/L for at least 7 days in 74% and 60%, respectively (*P* = 0.115).<br>• *Lancet Neurol*. 2008;7(2):136-144.[oo] Patients with CIDP received either Gamunex (n=58) or placebo (n=58) for 24 weeks. The percentage of adjusted-INCAT responders, defined as patients who maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through week 24, was 54% versus 21% in the Gamunex and placebo groups, respectively (difference of 33.5%; 95% CI, 15.4% to 51.7%; *P* = 0.002).<br>• *Clin Exp Immunol*. 2010;161(3):518-526.[pp] In an open-label trial, 32 patients aged 13 to 75 years with PI on stable Gamunex therapy received 2 IV infusions and then after a washout period of 7 to 10 days switched to a weekly infusion of subcutaneous Gamunex (dose equal to 137% of the previous weekly equivalent IV dose) for up to 24 weeks. The mean ratio of the AUC of plasma total IgG over the regular dosing interval of subcutaneous vs. IV administration at steady state was 0.89, which met non-inferiority criteria. No acute bacterial infections were reported during the study period.<br>• *J Clin Immunol*. 2016;36(6):600-9.[qq] Twelve pediatric patients aged 2 to 16 years old with a diagnosis of PI and on IgG replacement therapy received 2 IV infusions of Gamunex. A week after completion of the second infusion, patients received weekly subcutaneous Gamunex (dose equal to 137% of the previous weekly equivalent IV dose) for 12 weeks. The mean steady-state AUC ratio of the plasma total IgG over the regular dosing interval (subcutaneous/IV) was 1.05. No acute bacterial infections were reported during the study period. During the subcutaneous phase, 100% (n=11) of patients reported local infusion reactions and 81.8% (n=9) of patients reported non-infusion site reactions.<br>**Gammaplex**<br>• *Clin Exp Immunol*. 2010; 162(3): 510–5.[rr] Fifty subjects aged 9 to 78 years with PI were treated with Gammaplex 5% for 12 months at 21-day (22 subjects) or 28-day (28 subjects) dosing intervals. Doses ranged from 279 mg/kg to 799 mg/kg. During 12 months, no aSBIs occurred in any subject. The mean event rate of aSBIs per year was 0 (with an upper 1-sided 99% confidence interval of 0.101). The most common adverse reactions (>5%) observed were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain, and vomiting.<br>• *PLoS One*. 2014;9(6):e96600.[ss] Thirty-five patients aged 6 to 70 years with a diagnosis of ITP received 1 g/kg of Gammaplex 5% on 2 consecutive days. Safety and efficacy assessments occurred on days 3, 5, 9, 14, 21, 3, and 90. In the ITT population, 29 patients (82.9%) attained a platelet count of ≥50 x 109/L by Day 9 (lower limit of the 95% CI was 68.9%). The most common adverse drug reactions were headache, vomiting, and pyrexia.<br>• *Clin Exp Immunol.* 2016; 184(2): 228–236.[tt] Twenty-five children and adolescent patients aged 3 to 16 years with PI received Gammaplex 5% (at doses of 300–800 mg/kg/infusion) for 12 months, with a 3-month follow-up. Annual aSBI event rate in the ITT population was 0.09 (upper bound 99% CI of 0.36). The most common adverse reactions (>5%) observed were headache and sinusitis.<br>• *J Clin Immunol*. 2017; 37(3): 301–310.[uu] In a phase 3, open-label, multicenter, randomized, 2-period crossover bioequivalence and bridging study, the pharmacokinetics, safety, and tolerability of Gammaplex 5% and 10% were assessed in adults (n = 33, aged 17–55 years) and children (n = 15, aged 3–15 years) with PI. Adults received 5 infusions each of Gammaplex 5% and 10% during 2 different periods. Pediatric subjects received 5 Gammaplex 10% infusions only. The bioequivalence of Gammaplex 5% and 10% was met based on the 90% AUC0-28 ratio. The safety and tolerability were comparable.<br>**Octagam**<br>• *Hematology*. 2010;15(5):351-9.[vv] In a multicenter, open-label, single-arm study, 115 patients with ITP received Octagam 10% 1 g/kg daily on 2 consecutive days. In the ITT population, 92 patients (80%; 95% CI, 72.7% to 87.3%) met the primary efficacy endpoint of clinical response (an increase in platelet count to ≥50x109/L within 6 days of dosing). The most common treatment-related adverse events were headache (25%), pyrexia (14.7%), and increased heart rate, conservatively defined as ≥10 beats per minute (11%).<br>• *J Clin Immunol*. 2004;24(3):309-314.[ww] Patients (n = 46) with PI received cyclical Octagam for 12 months. The estimated infection rate was 0.1 aSBIs/subject/year.<br>• *Medicine*. 2021;100(1).[xx] ProDERM was a multicenter, double-blind, randomized, placebo-controlled study, in which patients with DM were randomized to receive 2 m/kg Octagam (n = 47) or placebo (n = 48) every 4 weeks. The primary outcome was the number of patients who had an increase of ≥ 20 points on the Total Improvement Score at week 16. At week 16, 78.7% of Octagam-treated patients met the primary outcome vs. 4.38% in the placebo group (*P* = .0008).<br>**Privigen**<br>• *J Peripher Nerv Syst*. 2013;18(2):130-140.[yy] In a multicenter, open-label, single-arm study, 28 patients with CIDP (13 were IVIG-pretreated) received an induction dose of Privigen (2 g/kg body weight) and up to 7 maintenance doses (1 g/kg body weight) at 3 week intervals. The overall responder rate, defined as improvement of ≥1 point on the adjusted INCAT disability scale was 60.7% (95% CI; 42.41% to 76.43%) (preset success criterion was a responder rate of ≥35%). The most common adverse events (>10%) were headache, pain in an extremity, hypertension, asthenia, leukopenia, and nausea.<br>• *J Clin Immunol.* 2009;29(1):137-144.[zz] In a multicenter, open-label, single-arm study, 80 patients with PI who had received regular IVIG therapy for at least 6 months prior to screening, received Privigen for 12 months. During the study period, 6 aSBIs occurred. The annual rate of aSBI was 0.08 and 0.09 in the ITT and PP populations, respectively. Headache was the most frequently reported adverse event with an incidence of 67.5%.<br>• *Hematology*. 2009;14(4):227-236.[aaa] In a multi-center, open-label, single-arm study, 57 patients with chronic ITP were enrolled and administered Privigen 1 g/kg on 2 consecutive days. Response, defined as an elevation of platelet count to ≥ 50 x 109/L within 7 days of the first infusion, occurred in 80.7% of patients (95% CI, 69.2% to 89.3%). Most common side effects were headache (66.7%) and fever (35.1%). |

Abbreviations: ABW = actual body weight; adjIBW = adjusted ideal body weight; aSBIs = acute serious bacterial infections; AUC = area under the curve; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = chronic lymphocytic leukemia; D5W = dextrose 5% in water; DM = dermatomyositis; IBW = ideal body weight; ILI = influenza like illness; IVIG = intravenous immune globulin; INCAT = inflammatory neuropathy cause and treatment; ITP = immune thrombocytopenic purpura; ITT= intent to treat; KS = Kawasaki syndrome; MMN = Multifocal motor neuropathy; NaCl = sodium chloride; PEG = polyethylene glycol; PI = primary immunodeficiency disease; PP = per protocol; SD = solvent/detergent; TE = Thromboembolic events; TSE = transmissible spongiform encephalopathies

## Appendix 1. SCIG side-by-side comparison

| Brand name | Cutaquig | Cuvitru | Gammagard Liquid | Gammaked[b] Gamunex-C | Hizentra | Hyqvia | Xembify |
|---|---|---|---|---|---|---|---|
| **Manufacturer** | Octapharma | Baxalta | Takeda | Grifols for Kedrion Grifols | CSL Behring | Baxalta | Grifols |
| **Dosage form** | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid | Ready-to-use liquid |
| **Concentration** | 16.5% | 20% | 10% | 10% | 20% | 10% IgG + 5% hyaluronidase | 20% |
| **SC FDA-approved indications (adult unless other specified)** | | | | | | | |
| *CIDP* | -- | -- | -- | -- | **X** | -- | -- |
| *PI* | **X** | **X** - ≥ 2 y | **X** | **X** | **X** - ≥ 2 y | **X** | **X** - ≥ 2 y |
| **Plasma source** | FDA-approved plasmapheresis centers | | | | | | |
| **Specific viral inactivation/ removal process** | • Cold ethanol fractionation<br>• Ultrafiltration<br>• Chromatography<br>• SD<br>• pH 4 treatment | • Cold ethanol fractionation<br>• Ion-exchange chromatography<br>• SD<br>• Nanofiltration (35nm)<br>• Low pH incubation | • SD<br>• Nanofiltration (35 nm)<br>• Low pH incubation | • Caprylate precipitation/ depth filtration<br>• Caprylate incubation<br>• Column chromatography<br>• Depth filtration<br>• Nanofiltration<br>• Low pH incubation | • Cold ethanol fractionation<br>• Octanoic acid fractionation<br>• Anion exchange chromatography<br>• Nanofiltration (20 nm)<br>• pH 4 incubation<br>• Depth filtration | • Cold ethanol fractionation<br>• Ion-exchange chromatography<br>• Low pH treatment<br>• Nanofiltration (35 nm)<br>• SD | • Cold ethanol fractionation<br>• Caprylate precipitation and filtration<br>• Caprylate incubation<br>• Anion-exchange chromatography<br>• Low pH incubation<br>• Nanofiltration |
| **Validated TSE removal steps** | No | No | No | Yes | Yes | No | Yes |
| **Pharmacology** | Subcutaneous immune globulins are sterile preparations of concentrated antibodies (immune globulins) recovered from pooled human plasma of healthy donors. These preparations provide replacement therapy for patients with immune deficiencies. | | | | | | |
| **Pharmacokinetics/stability** | | | | | | | |
| *Half-life (h)* | 49.3 (1.8 - 98.3)[c] | 105 (71 - 119)[c] | 35 (median) | 35[d] | Not available | 59 (36.1) d | Not available |

| Brand name | Cutaquig | Cuvitru | Gammagard Liquid | Gammaked[b] Gamunex-C | Hizentra | Hyqvia | Xembify |
|---|---|---|---|---|---|---|---|
| *Storage* | 2 - 8°C or ≤ 25°C<br>• Protect from light<br>• Do not freeze | 2 - 8°C or ≤ 25°C<br>• Protect from light<br>• Do not freeze | 2 - 25°C<br>• Do not freeze | 2 - 8°C or ≤ 25°C<br>• Do not freeze | ≤ 25°C<br>• Protect from light<br>• Do not freeze | 2 - 8°C or ≤ 25°C<br>• Protect from light<br>• Do not freeze | 2 - 8°C or ≤ 25°C<br>• Do not freeze<br>• Do not shake |
| *Shelf-life (mo)* | • 36 mo from date of manufacture if stored under refrigeration<br>• 6 mo at temperatures not to exceed 25°C | • 36 mo from date of manufacture if stored under refrigeration<br>• 24 mo at temperatures not to exceed 25°C | • 36 mo if stored under refrigeration<br>• 24 mo if stored at room temperature | • 36 mo from date of manufacture if stored under refrigeration<br>• 6 mo (any time prior to the expiration date) at temperatures not to exceed 25°C | • 30 mo from the date of manufacture if stored at room temperature | • 36 mo from the date of manufacture if stored under refrigeration<br>• 3 mo (during the first 24 mos) at temperatures not to exceed 25°C | • Shelf-life from the date of manufacture if stored under refrigeration determined by expiration date<br>• 6 mo (any time prior to the expiration date) at temperatures not to exceed 25°C |
| **Contraindications** | | | | | | | |
| *Anaphylaxis/ severe systemic reactions to human IG or other components* | X | X | X | X | X | X | X |
| *IgA deficiency with antibodies to IgA and a history of hypersensitivity* | X | X | X | X | X | X | X |
| *Other* | -- | -- | -- | -- | Hyperprolinemia Type I or II | Systemic hypersensitivity to hyaluronidase and albumin | -- |
| **Boxed warning** | Thrombosis may occur with immune globulin products. 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. For patients at risk for thrombosis, administer SCIG 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. | | | | | | |
| **Warnings and precautions** | May carry a risk of transmitting infectious agents due to human plasma origin, including (theoretically) Creutzfeldt-Jakob disease agent. Maybe associated with hemolytic anemia, thromboembolic events, transfusion-related acute lung injury, aseptic meningitis syndrome, hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia. IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Periodic monitoring of renal function and urine output is important in patients at risk for acute renal failure. | | | | | | |
| | Maltose content may potentially result in a falsely elevated glucose reading. | -- | -- | Due to risk of hematoma formation, do not administer subcutaneously in ITP | -- | Potential antibody development to PH20 (recombinant human hyaluronidase) | -- |

| Brand name | Cutaquig | Cuvitru | Gammagard Liquid | Gammaked[b] Gamunex-C | Hizentra | Hyqvia | Xembify |
|---|---|---|---|---|---|---|---|
| **Adverse reactions** | Adverse event profiles are often patient-specific. Brand, concentration, and rate of infusion may have an effect on patient tolerability. Most patients develop tolerance, but if side effects become intolerable, another brand of SCIG may be administered. | | | | | | |
| | Incidence ≥ 5%: Local infusion site reactions, headache, fever, diarrhea, dermatitis, asthma, and skin abrasion | Incidence ≥ 5%: Local infusion site reactions, headache, nausea, fatigue, diarrhea, and vomiting | **PI** (incidence ≥5%): Headache, fatigue, pyrexia, nausea, chills, rigors, pain in extremity, diarrhea, migraine, dizziness, vomiting, cough, urticaria, asthma, pharyngolaryngeal pain, rash, arthralgia, myalgia, oedema peripheral, pruritus, and cardiac murmur | **PI** (incidence ≥5%): Increased cough, rhinitis, pharyngitis, headache, asthma, nausea, fever, diarrhea, and sinusitis | Incidence ≥ 5%: Local infusion site reactions, headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, upper respiratory tract infection, rash, pruritus, vomiting, abdominal pain (upper), migraine, arthralgia, pain, fall and nasopharyngitis | Incidence ≥ 5%: Local infusion site reactions, headache, antibody formation against Recombinant Human Hyaluronidase (rHuPH20), fatigue, nausea, pyrexia, and vomiting | Incidence ≥ 5%: Local infusion site reactions, cough, and diarrhea |
| **Administration – Consult individual prescribing information for specific dosing guidance** | | | | | | | |
| *Route* | SC | SC | SC (PI)<br>IV (PI, MMN) | SC (PI)<br>IV (PI, ITP, CIDP) | SC | SC | SC |
| *Infusion site(s)* | Abdomen, thigh, upper arm, and/or upper leg/hip area; with at least 2 inches between sites, avoiding bony prominences | Abdomen, thigh, upper arm, or lateral hip; with at least 4 inches between sites, avoiding bony prominences | Abdomen, thigh, upper arm, or lower back; with at least 2 inches between sites, avoiding bony prominences | Abdomen, thigh, upper arm, or lateral hip; 2 inches between sites, avoiding bony prominences | Abdomen, thigh, upper arm, or side of upper leg/hip area; with at least 2 inches between sites, avoiding bony prominences | Abdomen or thighs; if 2 sites used, on opposite sides of the body avoiding bony prominences or scarred, inflamed, or infected areas | Abdomen, thigh, upper arm, sides, back, and/or lateral hip; with at least 2 inches between sites, avoiding bony prominences |
| *Number of infusion sites* | Up to 6 infusions sites simultaneously | Up to 4 infusion sites simultaneously | Up to 8 infusion sites simultaneously | • Adults: up to 8 infusion sites simultaneously<br>• Pediatrics: up to 6 infusion sites simultaneously | Up to 8 infusion sites simultaneously or up to 12 consecutively per infusion | Up to 2 infusion sites simultaneously | Up to 6 infusions sites simultaneously |
| *Switching from IVIG (dose adjustment factor)* | 1.4 | 1.3 (when switching from IVIG and Hyqvia) | 1.37 | 1.37 | 1.37 | Administer at the same dose and frequency as the previous IVIG dose (after initial dose titration) | 1.37 |
| *Switching from SCIG* | Maintain same weekly dose of prior SCIG therapy | Maintain same weekly dose of prior SCIG therapy (see above for switching from Hyqvia) | Not specified | Not specified | Maintain same weekly dose of prior SCIG therapy | 300 to 600 mg/kg every 3 - 4 weeks (after initial dose titration) | Maintain same weekly dose of prior SCIG therapy |

| Brand name | Cutaquig | Cuvitru | Gammagard Liquid | Gammaked[b] Gamunex-C | Hizentra | Hyqvia | Xembify |
|---|---|---|---|---|---|---|---|
| *Volume per site (mL/site)* | • Doses 1-6: ≤25<br>• Subsequent doses: ≤ 40 | • Doses 1 and 2:<br><40 kg ≤20<br>≥40 kg ≤60<br>• Subsequent doses: ≤60 | • <40 kg: 20<br>• ≥40 kg: 30 | Not specified | • Dose 1:<br>PI ≤15<br>CIDP ≤20<br>• Subsequent doses:<br>PI ≤25<br>CIDP ≤50 | • <40 kg: 300<br>• ≥40 kg: 600 | 25 |
| *Infusion rate (mL/h/site)* | • Doses 1-6: ≤20<br>• Subsequent doses: ≤25 | • Doses 1 and 2: 10 - 20<br>• Subsequent doses: ≤60 | • Dose 1:<br><40 kg 15<br>≥40 kg 20<br>• Subsequent doses:<br><40 kg 15-20<br>≥40 kg 20-30 | • Adults: 20<br>• Pediatrics:<br><25 kg 10<br>≥25 kg 15 (initial), 20 (maintenance) | • Dose 1:<br>PI ≤ 15<br>CIDP ≤20<br>• Subsequent doses:<br>PI ≤ 25<br>CIDP ≤50 | • Doses 1 and 2:<br><40 kg: 5, 10, 20, then 40 for 5-15 min each, followed by 80 for the remainder;<br>≥40 kg: 10, 30, 60, then 120 for 5-15 min each, followed by 240 for the remainder<br>• Subsequent 2 or 3 infusions:<br><40 kg: 10, 20, 40, then 80 for 5-15 min each, followed by 160 for the remainder;<br>≥40 kg: 10, 30, 120, then 240 for 5-15 min each, followed by 300 for the remainder | ≤25 |
| *Maximum infusion rate for all sites combined (mL/h/all sites combined)* | 100 | 240 | 240 | Not specified | Not specified | Not specified | Not specified |
| *Reconstitution/ dilution* | Do not dilute | Do not dilute | May be diluted with D5W | May be diluted with D5W | Do not dilute | Do not dilute | Do not dilute |
| *Reconstitution time* | -- | -- | -- | -- | -- | -- | -- |
| *Filter* | No | No | Optional | No | No | No | No |
| *Line flush* | Not available | Not available | 0.9% NaCl | D5W or 0.9% NaCl | Not available | D5W (if required) | Not available |
| **Content characteristics** | | | | | | | |
| *IgG (%)* | ≥96 | ≥98 | ≥98 | ≥98 | ≥98 | ≥98 | ≥98 |
| *IgA (mcg/ml)* | ≤600 | ≤800 | 37 | 46 | ≤50 | 37 (average) | <70[c] |
| *Albumin* | 0[c] | Not available | Not available | ≤ 2 mcg/mL | Not available | 1.0 mg/mL | Not available |

| Brand name | Cutaquig | Cuvitru | Gammagard Liquid | Gammaked[b] Gamunex-C | Hizentra | Hyqvia | Xembify |
|---|---|---|---|---|---|---|---|
| *PEG* | 0[c] | Not detectable[c] | None[d] | None[d] | Not available | Not detectable[c] | Not available |
| *Polysorbate 80* | Yes | No | No | No | Yes | No | Yes |
| *Stabilizer* | Maltose | Glycine | Glycine | Glycine | Proline | Glycine | Glycine |
| *Sugar content* | 79 mg/mL maltose | None | None | None | None | None | Not available |
| *Sodium content* | ≤30 mmol/L | None | None | Trace (<7 mEq/L)[d] | Trace amounts | None | Trace amounts[c] |
| *pH when reconstituted* | 5.0 – 5.5 | 4.6 – 5.1 | 4.6 – 5.1 | 4.0 – 4.5 | 4.6 – 5.2 | 4.6 – 5.1 | 4.1 – 4.8 |
| *Osmolality (mOsmol/kg)* | 310 – 380 | 280 – 292 | 240 – 300 | 258 | 210 – 290 mmol/L | 240 – 300 | 280 – 404 |
| **Interactions** | Passive transfer of antibodies with immunoglobulin may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella. Passive transfer of antibodies may lead to misinterpretation of the serologic test results. | | | | | | |
| **Latex-free** | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Tamper-evident** | Yes (cap) | Yes (cap)[c] | Yes[d] | Yes (shrink band) | Yes (vials)[c] | Yes (cap)[c] | Yes |
| **Vial size (g)** | 1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g | 1 g, 2 g, 4 g, 8 g, 10 g | 1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g | • Gamunex-C: 1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g<br>• Gammaked: 1 g, 2.5 g, 5 g, 10 g, 20 g | 1 g, 2 g, 4 g, 10 g | 2.5 g (200 units recombinant hyaluronidase), 5 g (400 units), 10 g (800 units), 20 g (1600 units), 30 g (2400 units) | 1 g, 2 g, 4 g, 10 g |
| **Prefilled syringe (g)** | -- | -- | -- | -- | 1 g, 2 g, 4 g | -- | -- |
| **Enhancements** | Peel-off label (lot number, expiration date) | Peel-off label (lot number, expiration date) | Peel-off label (lot number, expiration date | • Laser etched vial<br>• Integrated hangers for 4 larger vial sizes<br>• Peel-off label (lot number) | Peel-off label (lot number, expiration date) | Peel-off label (lot number, expiration date) | • Laser etched vials[c]<br>• Peel-off label (lot number, expiration date) |

Abbreviations: ABW = actual body weight; adjIBW = adjusted ideal body weight; aSBIs = acute serious bacterial infections; AUC = area under the curve; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = chronic lymphocytic leukemia; D5W = dextrose 5% in water; DM = dermatomyositis; IBW = ideal body weight; ILI = influenza like illness; IVIG = intravenous immune globulin; INCAT = inflammatory neuropathy cause and treatment; ITP = immune thrombocytopenic purpura; ITT= intent to treat; KS = Kawasaki syndrome; MMN = Multifocal motor neuropathy; NaCl = sodium chloride; PEG = polyethylene glycol; PI = primary immunodeficiency disease; PP = per protocol; SD = solvent/detergent; TE = Thromboembolic events; TSE = transmissible spongiform encephalopathies

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[b] A 10% solution can be prepared by using half the volume of diluent supplied.

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[e] For the 10% concentration, amount is doubled.

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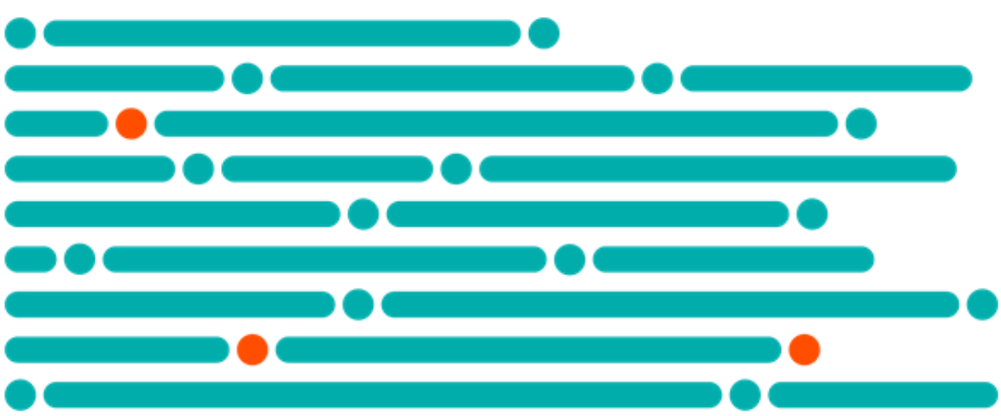

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