

### Intravenous Immune Globulins (IVIG) Side-by-Side Comparison

|  |  |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
|--|--|--|---|--|---|--|---|-------------------------|----------|------|----|-----------|----|----------|------|----------------|------------------|-------------------------------|---|----------------------|---|---|---|----------------------------|-----------------------|-----------------------|---|-----------------------|---|--|-----------------------|---------------------------------------|------------------------------|--|--|---|----------------|--|--|
| <b>Brand Name</b>                          | Carimune NF  | Flebogamma 5% DIF  | Gamunex 10%   | Gammagard S/D  | Gammagard Liquid 10%                              | Octagam 5%   | Privigen 10%  |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Manufacturer</b>                        | CSL Behring  | Grifols  | Talecris  | Baxter   | Baxter  | Octapharma   | CSL Behring   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>FDA-Approved Indications</b>            | acute and chronic ITP, PID   | PID  | ITP, PID  | ITP, PID, CLL, KS  | PID   | PID  | PID, chronic ITP                                    |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Plasma Source</b>                       | >16,000 donors   | U.S. volunteer donors via plasmapheresis   | Plasmapheresis  | Plasmapheresis 10,000 donors   | Plasmapheresis 10,000 donors                      | U.S. volunteer donors via plasmapheresis   | Plasmapheresis                                      |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Viral Inactivation/ Removal Process</b> | Depth filtration, pH 4/pepsin, nanofiltration  | Pasteurization, solvent/detergent, double sequential nanofiltration, fraction precipitation, PEG precipitation, pH 4 | Cold ethanol fractionation, pH 4.2, depth filtration, caprylate, chromatography | Cold ethanol fractionation, ultrafiltration, chromatography, solvent/detergent | Solvent/detergent, low pH, nanofiltration         | Cold ethanol fractionation, solvent/detergent, pH 4, ultrafiltration, chromatography | pH 4, nanofiltration, depth filtration              |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Pharmacology</b>                        | 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.   |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Pharmacokinetics/ Stability</b>         | <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: center;"><i>Half-life (days)</i></td> <td style="text-align: center;">21 to 23</td> <td style="text-align: center;">37.5</td> <td style="text-align: center;">35</td> <td style="text-align: center;">37.7 ± 15</td> <td style="text-align: center;">35</td> <td style="text-align: center;">25 to 40</td> <td style="text-align: center;">36.6</td> </tr> <tr> <td style="text-align: center;"><i>Storage</i></td> <td style="text-align: center;">Room temperature</td> <td style="text-align: center;">2 to 25°C; Protect from light</td> <td style="text-align: center;">Room temperature or Refrigerated; Do not freeze</td> <td style="text-align: center;">≤25°C; Do not freeze</td> <td style="text-align: center;">Room temperature or Refrigerated; Do not freeze</td> <td style="text-align: center;">Room temperature or Refrigerated; Do not freeze</td> <td style="text-align: center;">Room temperature; Do not freeze; Protect from light</td> </tr> <tr> <td style="text-align: center;"><i>Shelf-life (months)</i></td> <td style="text-align: center;">24; preservative-free</td> <td style="text-align: center;">24; preservative-free</td> <td style="text-align: center;">6 to 36 (depending on storage); preservative-free</td> <td style="text-align: center;">24; preservative-free</td> <td style="text-align: center;">9 to 36 (depending on storage); preservative-free</td> <td style="text-align: center;">18 to 24 (depending on storage); preservative-free</td> <td style="text-align: center;">24; preservative-free</td> </tr> <tr> <td style="text-align: center;"><i>Stability after reconstitution</i></td> <td style="text-align: center;">24 hours under refrigeration</td> <td style="text-align: center;">Not applicable; Use promptly after entering vial</td> <td style="text-align: center;">Not applicable; Use promptly after entering vial</td> <td style="text-align: center;">24 hours under refrigeration; otherwise begin administration within 2 hours</td> <td style="text-align: center;">Not applicable</td> <td style="text-align: center;">Not applicable; Use promptly after entering vial</td> <td style="text-align: center;">Not applicable; Use promptly after entering vial</td> </tr> </table> |  |   |  |   |  |   | <i>Half-life (days)</i> | 21 to 23 | 37.5 | 35 | 37.7 ± 15 | 35 | 25 to 40 | 36.6 | <i>Storage</i> | Room temperature | 2 to 25°C; Protect from light | Room temperature or Refrigerated; Do not freeze | ≤25°C; Do not freeze | Room temperature or Refrigerated; Do not freeze | Room temperature or Refrigerated; Do not freeze | Room temperature; Do not freeze; Protect from light | <i>Shelf-life (months)</i> | 24; preservative-free | 24; preservative-free | 6 to 36 (depending on storage); preservative-free | 24; preservative-free | 9 to 36 (depending on storage); preservative-free | 18 to 24 (depending on storage); preservative-free | 24; preservative-free | <i>Stability after reconstitution</i> | 24 hours under refrigeration | Not applicable; Use promptly after entering vial | Not applicable; Use promptly after entering vial | 24 hours under refrigeration; otherwise begin administration within 2 hours | Not applicable | Not applicable; Use promptly after entering vial | Not applicable; Use promptly after entering vial |
| <i>Half-life (days)</i>                    | 21 to 23   | 37.5   | 35  | 37.7 ± 15  | 35  | 25 to 40   | 36.6  |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <i>Storage</i>                             | Room temperature   | 2 to 25°C; Protect from light  | Room temperature or Refrigerated; Do not freeze                                 | ≤25°C; Do not freeze   | Room temperature or Refrigerated; Do not freeze   | Room temperature or Refrigerated; Do not freeze                                      | Room temperature; Do not freeze; Protect from light |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <i>Shelf-life (months)</i>                 | 24; preservative-free  | 24; preservative-free  | 6 to 36 (depending on storage); preservative-free                               | 24; preservative-free  | 9 to 36 (depending on storage); preservative-free | 18 to 24 (depending on storage); preservative-free                                   | 24; preservative-free                               |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <i>Stability after reconstitution</i>      | 24 hours under refrigeration   | Not applicable; Use promptly after entering vial   | Not applicable; Use promptly after entering vial                                | 24 hours under refrigeration; otherwise begin administration within 2 hours    | Not applicable                                    | Not applicable; Use promptly after entering vial                                     | Not applicable; Use promptly after entering vial    |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Contraindications</b>                   | Patients with IgA deficiencies, antibodies to IgA, and previous severe systemic reactions to IVIG therapy. Privigen® is contraindicated in patients with hyperproliferemia.  |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Precautions/ Warnings</b>               | <b>Black Box Warning:</b> 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. May contain infectious agents due to human plasma origin. Inflammatory reactions, characterized by a rise in temperature, chills, nausea, and vomiting, and anaphylactoid and hypersensitivity reactions may occur. May cause hemolytic anemia, thromboembolic events, transfusion-related acute lung injury (noncardiogenic pulmonary edema), and aseptic meningitis syndrome. Pregnancy category C; unknown effects when used in nursing mothers.   |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Adverse Events (Incidence)</b>          | Adverse event profiles are often patient-specific. Brand, concentration, and rate of infusion may have an affect on patient tolerability. Common side effects include hypotension, hypertension, and headache, which can be diminished by reducing rate of infusion. 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.   |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
|  | ITP: 2.9%; PID: 10%  | 8% within 72 hours   | Headache (8%), cough increased (7%), fever (1%)                                 | ITP: 75% experience headache; PID: 6%; CLL: 1.3%; KS: 5.4%                     | Headache (6.9%), fever (2.3%)                     | PID: 15%   | PID: 23.8%; ITP: headache (36%), fever (19.3%)      |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Drug Interactions</b>                   | 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 and 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.  |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Administration Considerations</b>       | <i>See individual package inserts for more specific dosing guidelines.</i>   |  |   |  |   |  |   |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Maximum Infusion Rate</b>               | See calculations in package insert   | 0.1 mL/kg/min  | 0.08 mL/kg/min  | 4 mL/kg/hr (5% concentration); 8 mL/kg/hr (10% concentration)                  | 5 mL/kg/hr  | 0.07 mL/kg/min   | 0.08 mL/kg/min (PID)<br>0.04 mL/kg/min (ITP)        |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Infusion Rate in Renal Disease</b>      | <2 mg/kg/min   | <0.06 mL/kg/min  | <0.08 mL/kg/min   | <4 mL/kg/hr (5% concentration); <2 mL/kg/hr (10% concentration)                | <2 mL/kg/hr                                       | <0.07 mL/kg/min  | <0.02 mL/kg/min                                     |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Reconstitution Time</b>                 | Several minutes up to 20 minutes   | Liquid/ready-to-use  | Liquid/ready-to-use (may be diluted to 5% with D5W)                             | Less than 5 minutes at room temperature; more than 20 minutes if cold          | Liquid/ready-to-use                               | Liquid/ready-to-use  | Liquid/ready-to-use                                 |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |
| <b>Filter</b>                              | No filter required   | Filter recommended   | No filter required  | Filter required  | Filter optional                                   | Filter required  | No filter required                                  |                         |          |      |    |           |    |          |      |                |                  |                               |   |                      |   |   |   |                            |                       |                       |   |                       |   |  |                       |                                       |                              |  |  |   |                |  |  |

| Brand Name                     | Carimune NF   | Flebogamma 5% DIF                     | Gamunex                             | Gammagard S/D                                       | Gammagard Liquid 10%                             | Octagam 5%                                       | Privigen 10%                         |
|--------------------------------|---|---------------------------------------|-------------------------------------|---|--|--|--------------------------------------|
| <b>Content/Characteristics</b> |   |                                       |                                     |   |  |  |                                      |
| <b>IgA (mcg/mL)</b>            | Trace   | < 50                                  | 46                                  | ≤ 2.2 (5% concentration); <1 (separate 5% solution) | 37   | ≤ 200  | <25                                  |
| <b>IgG (%)</b>                 | > 96  | > 99                                  | > 98                                | ≥ 90  | ≥ 98   | > 96   | 98                                   |
| <b>IgM (mcg/mL)</b>            | Trace   | Trace                                 | < 2                                 | Trace   | Trace  | ≤100   | Not available                        |
| <b>Albumin</b>                 | 0   | 2 mcg/mL                              | < 20 mcg/mL                         | < 3 mg/mL   | 0  | Not available                                    | Trace                                |
| <b>Sugar</b>                   | 5% sucrose  | 50 mg/mL D-sorbitol                   | 0 (glycine stabilized)              | 2% glucose  | 0 (glycine stabilized)                           | 10% maltose                                      | 0 (L-proline stabilized)             |
| <b>Sodium</b>                  | < 20 mg sodium chloride per g protein   | < 3.2 mEq/L (<0.02%)                  | Trace                               | 0.85%   | 0  | ≤ 30 mmol/L                                      | Trace                                |
| <b>pH when liquid</b>          | 6.6 ± 0.2   | 5 – 6                                 | 4 – 4.5                             | 6.8 ± 0.4   | 4.6 – 5.1  | 5.1 – 6  | 4.6 – 5                              |
| <b>Osmolality</b>              | In normal saline:<br>3%: 498 mOsm/kg<br>6%: 690 mOsm/kg<br>9%: 882 mOsm/kg<br>12%: 1074 mOsm/kg   | 342 – 350 mOsm/L                      | 256 ± 14 mOsm/kg                    | 5%: 636 mOsm/L<br>10%: 1250 mOsm/L                  | 240 – 300 mOsm/kg                                | 310 – 380 mOsm/kg                                | 240 – 440 mOsmol/kg                  |
| <b>Recommendations</b>         | The differences between the products, and the factors to consider when choosing a product, include production process, efficacy, safety, tolerability, and convenience of product formulation. The production and purification processes, while necessary, often affect the biological activity of the final product. While use of any biological product is at risk for contamination with infectious agents, the viral inactivation processes used for Gamunex® and Carimune NF® are the only that have been shown to remove pathogenic prions in addition to viruses. Use of licensure trials to determine efficacy of IVIG products is limited because they have historically been non-comparative, small, lacking in well-defined clinical endpoints, and not based on strong statistical trial design. Tolerability varies between patients and products due to parameters such as sodium, concentration, fluid volume necessary for reconstitution, osmolality, sugar, IgA content, and pH. When considering IVIG therapy, patient characteristics such as presence of IgA deficiencies, cardiac impairment, renal dysfunction, and risk of stroke must be considered. For treatment of ITP, glucocorticoids or anti-D (e.g., WinRho®) may be appropriate (see <i>American Society of Hematology ITP Guidelines</i> available at <a href="http://www.hematology.org/policy/guidelines/idiopathic.cfm">www.hematology.org/policy/guidelines/idiopathic.cfm</a> ). While there may be differences between the products in efficacy and tolerability, ultimately product availability may be the determining factor. At this time, Talecris, the manufacturer of Gamunex®, is experiencing shortages in human plasma which will result in a reduced supply of IVIG to the entire U.S. market well into 2008.  |                                       |                                     |   |  |  |                                      |
| <b>Studies</b>                 | <ul style="list-style-type: none"> <li>Ochs HD, Pinciaro PJ, Octagam Study Group. <i>J Clin Immunol.</i> 2004;24:309-14. Patients (n=46) with PID received cyclical Octagam® for 12 months. The estimated infection rate was 0.1 serious infection/subject/year.</li> <li>Jibiki T, Terai M, Kurosaki T, et al. <i>Eur J Pediatr.</i> 2004;163:229-33. Patients with acute Kawasaki disease (n=46) were treated with IVIG combined with dexamethasone for 3 days, followed by IVIG plus low-dose aspirin. Outcomes were compared to a historical control group of 46 patients treated with IVIG and high-dose aspirin. Post-treatment C-reactive protein levels and duration of fever was significantly lower in the dexamethasone group (p=0.033 and p=0.015, respectively). Two patients in each group developed coronary artery aneurysms.</li> <li>Bussel JB, Eldor A, Kelton JG, et al. <i>Thromb Haemost.</i> 2004;91:771-8. Investigators compared IVIG caprylate (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 x10<sup>9</sup>/L within 7 days of dosing in 90% and 83%, respectively; counts were maintained above 50 x10<sup>9</sup>/L for at least 7 days in 74% and 60%, respectively (p=0.115). Fewer patients receiving IVIG caprylate required corticosteroids beyond day 7 (p=0.02).</li> <li>Roifman CM, Schroeder H, Berger M, et al. <i>Int Immunopharmacol.</i> 2003;3:1325-33. Investigators compared IVIG caprylate (Gamunex®) with a solvent/detergent-treated product (Gamimune N®) in patients with PID (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).</li> <li>Wolf HH, Davies SV, Borte M, et al. <i>Vox Sang.</i> 2003;84:45-53. Investigators compared nanofiltered IVIG (IVIG-N) with its parent compound Sandoglobulin® in patients with ITP (n=27) and PID (n=36). In the ITP group, a similar number of patients experienced platelet increases to above 50 x10<sup>9</sup>/L (p=0.123). In the PID group, a similar number of patients missed days at work/school (p=0.805).</li> <li>Godeau B, Chevret S, Varet B, et al. <i>Lancet.</i> 2002;359:23-9. Adult patients (n=122) with severe ITP were randomized to receive IVIG or high-dose methylprednisolone on days 1 – 3, and then to receive oral prednisone or placebo on days 4 – 21. Patients receiving IVIG experienced significantly more days with platelet counts above 50 x10<sup>9</sup>/L (18 vs. 14 days, p=0.02) compared to those who received methylprednisolone plus prednisone (18.5 vs. 17.5 days, p=0.005).</li> </ul> |                                       |                                     |   |  |  |                                      |
| <b>Available Dosage Forms</b>  | Lyophilized: 3 g, 6 g, 12 g   | Liquid: 0.5 g, 2.5 g, 5 g, 10 g, 20 g | Liquid: 1 g, 2.5 g, 5 g, 10 g, 20 g | Lyophilized: 2.5 g, 5 g, 10 g; Solution: 5 g, 10 g  | Liquid (latex-free): 1 g, 2.5 g, 5 g, 10 g, 20 g | Liquid (latex-free): 1 g, 2.5 g, 5 g, 10 g, 25 g | Liquid (latex-free): 5 g, 10 g, 20 g |
| <b>Cost</b>                    |   |                                       |                                     |   |  |  |                                      |

ITP, immune thrombocytopenic purpura; PID, primary immunodeficiencies; CLL, chronic lymphocytic leukemia; KS, Kawasaki syndrome; PEG, polyethylene glycol; Ig, immunoglobulin; D5W, dextrose 5% in water

*Disclaimer: This chart is to be utilized for informational purposes only and by competent healthcare professionals. This chart should be utilized in conjunction with pertinent clinical and situational data. While every effort has been made to ensure the accuracy and completeness of the information presented in this chart, the reader is advised that the authors, editor, or publisher cannot be responsible for the currency of the information, for any errors, omissions, or any consequences that may arise. All supplied information may be found in the respective FDA-approved product information.*