

Subject: Intravenous Immune Globulin (IVIg) Therapy for Solid Organ Transplant	Original Effective Date: 02/02/2015
Policy Number: MCP-237	Revision Date(s): Q3 2019
Review Date(s): 12/15/2016, 6/22/2017, 3/10/2018; Q3 2020; Q4 2020	
MCPC Approval Date: 3/10/2018	
P&T Approval Date: Q3 2019, Q4 2020	

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DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses **Intravenous Immune Globulin (IVIg) for Solid Organ Transplantation** when appropriate criteria are met.

The intent of this policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Abbreviations:

- *Immune globulin, intravenous (human)*: Referred to as IVIg since this term is commonly used by clinicians, although the abbreviation used by industry and various regulatory agencies is IGIV
- *Immune globulin, subcutaneous*: Abbreviated as subcutaneous immune globulin (SCIg)

Refer to **MCP-043 for Intravenous infusion Immune Globulin (IVIg)** requests which address the coverage of immune globulin products FDA-approved for intravenous infusion (IVIg) when appropriate criteria are met.

Refer to **MCP-268 for Subcutaneous Immune Globulin (SCIg) therapy** requests which address the coverage of immune globulin products FDA-approved for subcutaneous infusion for the treatment of primary immune deficiency.

IMMUNE GLOBULIN

Immune globulins are components of the immune system. There are several types of immune globulin produced by the body (e.g., IgA, IgD, IgE, IgG, IgM). Immune globulins are used as replacement therapy to promote passive immunity in patients with primary humoral immunodeficiency diseases. Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Three formulations of human IgG are available depending on the route of delivery:

Intravenous immunoglobulin (IVIg)

- Produced by extraction of Ig fractions from blood from at least 1,000 donors; a single infusion of IVIg can be produced from the plasma of 2000 to 60,000 healthy individuals.
- Affects humoral and cell-based immunity through multiple pathways, without a single dominant mechanism
- Suppresses antibody production, has anti-idiotypic activity, interferes with co-stimulatory molecules including cytokines and chemokines, and inhibits activation of complement and formation of the membrane attack complex
- Modulates the expression and function of Fc receptors on macrophages and alters the activation, differentiation, and effector functions of T-cells.

Subcutaneous infusion (SCIg): Refer to MCP-268

SCIg is used for treating patients with primary immunodeficiencies, a genetic basis for more than 80 different types of primary immunodeficiencies has been discovered, the most common being primary antibody deficiency that is associated with low levels or total lack of normal circulating immunoglobulins. With SCIg, it is possible for patients to self-administer the therapy.

Intramuscular (IMiG) depot injections has been largely abandoned in the United States because volume constraints and pain preclude delivery of sufficient products weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections. Thus, this policy focuses on intravenous immune globulin for conditions that typically would be treated in an outpatient setting.

Comparison of SCIg with IVIg

- Immune globulin products specifically intended for subcutaneous (SC) and intramuscular (IM) administration are generally more concentrated than those designed for intravenous (IV) use, allowing more immune globulin to be administered in lower volumes.
 - Generally, many 10% IVIg solutions can be administered subcutaneously or intravenously, but more concentrated products (e.g., 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse events and provides more stable serum IgG levels. In contrast, SCIG has not been studied as extensively in autoimmune and inflammatory disorders.
 - IVIg is used when high doses are desired (e.g., 2 g/kg) in acute situations, such as in the management of Kawasaki disease, Guillain-Barré syndrome, and immune thrombocytopenia.
- IVIg infusions may be preferable for patients who require faster increase of trough level at initiation
- SCIG is associated with more stable serum Ig concentrations and advantageous for patients with poor venous access due to no need for indwelling venous catheter, particularly in patients with poor venous access
- Appendix 1: Comparison of IV and Subcutaneous Immunoglobulin Therapy

Immune globulin therapy is derived from the pooled plasma of thousands of donors and contains primarily (>98 %) human immunoglobulin G (IgG) with trace amounts of IgA and IgM. The products differ by route of administration [intravenous (IV) or subcutaneous (SC)], specific titers of each IgG subclass, viral inactivation processes, and additives such as sucrose and sodium. While all immune globulins have comparable efficacy in the treatment of immune deficiencies, the products are not interchangeable. **Selection of product should take into consideration various patient factors including diagnosis, condition and severity, individual comorbidities, available alternative treatments, and previous response to intravenous immune globulin therapy.**

Currently, there is no evidence of efficacy differences among the different IVIg products. However, there are potential differences in adverse effects among the different products. Patients with renal dysfunction, diabetes, sepsis, or age >65 years are at increased risk of developing kidney problems if a sucrose-containing product is used. In general, products with higher IgA content are associated with increased adverse effects. There is a higher chance of adverse effects if the IVIg product is switched after establishing therapy with a particular product.

Immune globulin preparations are available as pre-mixed liquids or lyophilized powders with varying concentrations of IgG. The manufacture of commercial immune globulin products from pooled plasma is a complex multistep process consisting of fractionation, purification, stabilization, virus inactivation, and virus removal and as a result, immune globulin products differ with respect to formulation and composition. Product characteristics such as content (e.g., IgA concentration, stabilizer), volume, and osmolality may be important considerations for some patients. However, **comparative data are lacking, and it is not known whether one specific product is superior for a particular disease or clinical setting. There is a lack of reliable evidence that any one brand of parenteral immunoglobulin is superior to other brands for medically necessary indications.**

Adjustments of dosage, frequency, site of administration, and duration of therapy must be consistent and supported by FDA-approved labeling for member's condition and severity, availability of alternative treatments, and prior response to immune globulin therapy.

Solid Organ Transplantation

Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction

(AbMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AbMR does not, and, as such, has also been referred to as “steroid-resistant rejection.”

- The risk of AbMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient’s serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool.
- The percentage of PRA is the percentage of positive reactions. Those with a PRA greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of ABMR.
- As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AbMR, often in conjunction with plasma exchange. For instance, in patients at high risk for AbMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AbMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AbMR develops.

Treatment

- The aim of immunosuppression in clinical practice is to control an undesirable immune response while avoiding, if possible, the complications of immunodeficiency. The effect can be achieved by ablation (i.e., irreversibly damaging immune tissue); by altering lymphocyte location and traffic; by altering lymphocyte or dendritic cell function; or by affecting lymphokines. These interventions may be physical (i.e., by irradiation, plasmapheresis, photopheresis) or pharmacological (i.e., IVIg).
- Patients with high levels of "anti-donor" antibodies often have very high rejection rates after transplant, especially in kidney transplant. Rejection risks are very high for a patient whose immune system has been exposed to "non-self" human leukocyte antigens (HLA). Exposure to HLAs may occur in a number of ways, including prior organ transplant or blood transfusions.
- IVIg increases a highly sensitized patient's chance of successful transplant. IVIg is a new immune-modulating therapy that can reduce high antibody levels and improve transplant rates. IVIg helps by modifying the immune system rather than suppressing it.
- IVIg is given while a highly sensitized patient waits for transplant, with the goal of decreasing their overall level of sensitization and therefore increasing the possibility that a donor kidney would be acceptable to their immune system.

FDA INDICATIONS

FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare. The covered FDA-approved indications are conditions that are considered medically necessary; however, it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the

discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria. Molina Healthcare reserves the right to update this Policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

This policy only addresses the coverage of Intravenous Immune Globulin (IVIg) for SOLID ORGAN TRANSPLANTATION when appropriate criteria are met.

BRAND NAME	ROUTE	PID	ITP	CLL	CIDP	KD	MMN
Intravenous							
Asceniv (FDA-approved April 2019)	IV	X					
Bivigam	IV	X					
Carimune NF	IV	X	X				
Flebogamma 5% DIF	IV	X					
Flebogamma 10% DIF	IV	X	X				
Gammagard S/D (5% or 10% when reconstituted)	IV	X	X	X		X	
Gammaplex 5% or 10%	IV	X	X				
Octagam 5%	IV	X					
Octagam 10%	IV		X				
Panzyga 10%	IV	X	X				
Privigen 10%	IV	X	X		X		
Intravenous OR Subcutaneous							
*Gammagard Liquid 10%	IV/SC	X					X
*Gammaked 10%	IV/SC	X	X		X		
*Gamunex-C 10%	IV/SC	X	X		X		
Subcutaneous Immune Globulin (SCIg)							
Hizentra 20%	SQ	X			X		
HyQvia 10%	SQ	X					
Cutaquig 16.5%	SQ	X					
Cuvitru 20%	SQ	X					
Xembify 20%	SQ	X					

PI: Primary Immunodeficiency; ITP: Immune Thrombocytopenia; CIDP: Chronic Inflammatory Demyelinating Polyneuropathy; CLL: Chronic Lymphocytic Leukemia; KD: Kawasaki Disease; MMN: Multifocal Motor Neuropathy
 *Gammaked, Gamunex-C, and Gammagard Liquid are approved for both intravenous and subcutaneous use for treatment of PID and when administered subcutaneously, are FDA-approved for the treatment of PID only. NOTE: Gammagard Liquid, Gammaked and Gamunex-C are not approved for SQ use in patients with ITP or CIDP.

§The following products do not contain sucrose: Gammaplex, Bivigam, Octagam 10%, Gamunex-C, Gammagard Liquid, Gammagard S/D, Gammaked, Flebogamma 5% DIF, Flebogamma 10% DIF, Privigen, and Hizentra

⌘ **Dosage Forms Considerations**

- Carimune NF may contain a significant amount of sodium and also contains sucrose.
- Cutaquig and Octagam contains maltose.
- Gammagard S/D may contain a significant amount of sodium and also contains glucose.

- Hyqvia Kit is supplied with a Hyaluronidase (Human Recombinant) component intended for injection prior to Immune Globulin administration to improve dispersion and absorption of the Immune Globulin.

⌘ Each product varies with FDA-approved indications.

⌘ Currently there are six (6) indications that are FDA approved for specific Ig products:

- Primary Immunodeficiency Diseases (PID) [includes, but are not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies]
- Idiopathic thrombocytopenic purpura (ITP)
- B-cell chronic lymphocytic leukemia (CLL)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Kawasaki Disease (KD)
- Multifocal Motor Neuropath (MMN)

SCIg products are currently only FDA approved for the **treatment of PID and CIDP (Hizentra only)**
Hizentra is the first and only SCIg approved for the treatment of CIDP (March 2018)

⌘ All conditions are FDA approved for the intravenous route. IVIg products will not be authorized for subcutaneous use, unless FDA approved for that route of administration.

⌘ All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID).

- Immune globulin is the standard treatment for PID. PID includes, but are not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Black Box Warnings

***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. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer 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 and acute renal failure (excluding Cuvitru, Hizentra, HyQvia, and GamaSTAN S/D)** may occur in predisposed patients with immune globulin intravenous IV products. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving immune globulin IV products containing sucrose. (Note: The following products do not contain sucrose: BIVIgam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam 5%, Octagam 10%, Panzyga, and PrIVIgen.) For patients at risk of renal dysfunction or acute renal failure, administer immune globulin IV products at the minimum concentration dose and infusion rate practicable. Ensure adequate hydration in patients before administration.*

CLASSIFICATION: Immunoglobulins

Drug shortages In August 2019, FDA released a statement addressing the issues of product shortages along with a list of the products with limited availability. IG products with a supply that is not able to keep pace as the reason for the shortages. Its recommendations for healthcare providers are to develop a system to determine which patients should receive priority treatment and to consider adding additional products to their formularies to use during times of shortages.

One or more forms of this drug may be in short supply or unavailable. Refer to the following for additional information: [ASHP FDA](#)

**Links will be updated with policy with annual review or revision.*

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Solid Organ Transplantation

Intravenous Immune Globulin (IVIg) may be authorized for members who meet **ALL** the following criteria [ALL]

1. Prescriber specialty [ONE]

- Prescribed by, or in consultation with, a board-certified physician affiliated with a transplant center or Transplantation Medicine Specialist. Submit consultation notes if applicable.
- Cytomegalovirus infection prophylaxis associated with organ transplantation: Prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

2. Diagnosis/Indication [ONE]

Prescribed for ONE (1) of the following (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*) and medication usage must be supported by documentation from the member's medical records:

- Prescribed for Solid Organ Transplantation for ONE (1) of the following conditions: [ONE]
 - **PRIOR** to solid organ transplant for prevention of acute rejection (pre- and peri-operative):
For prevention of antibody-mediated rejection prior to solid organ transplant, or in the peri-operative period, for patients at **high-risk** for antibody-mediated rejection [including highly sensitized patients, and those receiving an ABO-incompatible organ]
 - **POST** solid-organ transplant: [A OR B]
 - A. Treatment of antibody-mediated (humoral) rejection following solid organ transplant: Confirmation by either biopsy or presence of panel reactive antibodies (PRAs), if used in combination with plasmapheresis

B. Transplant recipients at high-risk for cytomegalovirus infections (CMV), OR for treatment of CMV pneumonitis in combination with antiviral therapy

- ◆ *Prophylaxis with intravenous Cytomegalovirus Intravenous Immune Globulin (CMV-IG; Cytogam[®]) has been demonstrated to reduce the morbidity associated with CMV disease in CMV-seronegative kidney, liver, pancreas, lung, and heart transplant recipients who receive organs from seropositive donors. Prophylaxis with the globulin should be considered for all CMV-seronegative transplant patients scheduled to receive kidneys, liver, pancreas, lung and heart from cytomegalovirus-seropositive donors. This recommendation should apply to recipients of cadaveric transplants as well as recipients of transplants from living related donors [Micromedex; Cytomegalovirus Immune Globulin, Human].*

3. Age/Gender/Other restrictions [ALL APPLICABLE]

- Requests post-transplant: For treatment 100 days or more post-transplant ONLY (not applicable to CMV infection prophylaxis requests) [ONE]
 - IgG less than 400mg/dL
 - OR
 - Documented CMV, EBV or RSV infection

- Requests **PRIOR** to kidney transplant ONLY:

Treatment is prescribed for member with high levels of "anti-donor" antibodies [i.e., patients highly sensitized to the tissue of the majority of living or cadaveric donors because of "non-self" human leukocyte antigen (HLA) or ABO incompatibility]. Documentation required.

- ◆ *To reduce the risk of acute antibody-mediated rejection, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies.^A (The National Advisory Committee on Blood and Blood Products and Canadian Blood Services, 2010)*

4. Step/Conservative Therapy/Other condition Requirements

N/A

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Anaphylactic or severe systemic reaction to human immune globulin or components of the product

- IgA deficiency with antibodies against IgA and a history of hypersensitivity; IG products contain trace amounts of IgA
- Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established
- Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections (IM)

Specific product indication [ANY]

- Octagam: Contraindicated in patients with acute hypersensitivity reaction to corn.
- Gammaplex and Flebogamma: Contraindicated in those with intolerance to any component of the product (i.e. intolerance to fructose). Gammaplex is also contraindicated in infants and neonates for whom sucrose or fructose tolerance has not been established.
- Flebogamma: Contraindicated or intolerance to any component of Flebogamma, such as sorbitol (i.e., intolerance to fructose)
- Privigen and Hizentra: Contraindicated in patients with hyperprolinemia (type I or II); Hizentra[®] and Privigen[®] contain the stabilizer L-proline.

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

- Date of transplant and IVIG treatment period requested
- Medical record documentation confirms the member has been definitively diagnosed (by an appropriate specialist) with one of the listed diagnosis above (#2)

REAUTHORIZATION /CONTINUATION OF THERAPY

Intravenous Immune Globulin (IVIg) may be authorized for continuation of therapy if meet **ALL** the following criteria are met: [ALL]

1. Initial Coverage Criteria

- Member currently meets ALL initial coverage criteria

2. Compliance

- No persistent or uncorrectable problems with adherence to IVIg treatment

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- Documentation of **stabilization or clinical improvement** as evidenced by physical findings and /or clinical symptoms following the initial IVIg treatment period
- Member is closely followed by the prescriber/specialist, and treatment response has clearly defined endpoints to measure effectiveness

4. Discontinuation of Treatment [ANY]

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Anaphylactic or severe systemic reaction to human immune globulin or components of the product
- IgA deficiency with antibodies against IgA and a history of hypersensitivity; IG products contain trace amounts of IgA
- Hereditary intolerance to fructose, including infants and neonates for whom sucrose or fructose tolerance has not been established
- Severe thrombocytopenia or any coagulation disorder which would contraindicate IM injections (IM)

Specific product indication [ANY]

- Octagam: Contraindicated in patients with acute hypersensitivity reaction to corn.
- Gammaplex and Flebogamma: Contraindicated in those with intolerance to any component of the product (i.e. intolerance to fructose). Gammaplex is also contraindicated in infants and neonates for whom sucrose or fructose tolerance has not been established.
- Flebogamma: Contraindicated or intolerance to any component of Flebogamma, such as sorbitol (i.e., intolerance to fructose)
- PrIVIgen and Hizentra: Contraindicated in patients with hyperprolinemia (type I or II); Hizentra[®] and PrIVIgen[®] contain the stabilizer L-proline.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

- IVIg: [AS APPLICABLE]
 - Single Dose: Up to 2 g/kg to a maximum of 140 g as a single dose
 - Recurrent Dose: 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/8 week period

- IVIg with plasma exchange: 0.1 to 0.5 g/kg which may be given in divided doses up to a total maximum dose of 2g/Kg/4 week period
- ◆ *The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.*
- ☐ Cytomegalovirus Immune Globulin Intravenous (Cytogam): 150 milligrams/kilogram/dose should not be exceeded
- NOTE:** Refer to Appendix 2 for additional dosing information on CMV-IG
 - ◆ *No standardized dose used for CMV-Ig in the literature*
 - ◆ *No trials comparing efficacy of IVIg and CMV-Ig for treatment. There is no clear evidence that CMV-Ig provides advantage over IVIg for treatment of CMV disease, and IVIg has also shown in some trials to be effective for adjunctive treatment of CMV pneumonia.*

2. Authorization Limit [ALL]

- ☐ Quantity limit: [ONE]
 - **PRIOR** to Transplant:
 - Prevention of acute rejection (pre- and peri-operative): Up to FOUR (4) doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant. Maximum of 8 doses. Authorization duration: 3 months
 - **POST** Transplant:
 - Treatment of antibody-mediated (humoral) rejection: ONE (1) dose, once per rejection episode. Authorization duration: 2 weeks
 - OR
 - Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: Maximum recommended total dosage per infusion is 150 mg IG/kg; max rate: 60mg/kg/hr
- ☐ Duration of initial authorization: Dependent on individual diagnosis [AS APPLICABLE]
 - **PRIOR** to Transplant: 3 months
 - **POST** Transplant: [1 OR 2]
 - 1) Treatment of antibody-mediated (humoral) rejection: 2 weeks
 - OR
 - 2) Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: 3 months
- ☐ Re-authorization for continuation of treatment is dependent on individual diagnosis as follows: [ONE]

- Prevention of acute rejection (pre- and peri-operative): Further authorization will be reviewed as Post-Transplant “Treatment of antibody-mediated (humoral) rejection”
 - Treatment of antibody-mediated (humoral) rejection: Documented improvement from previous course and confirmation of another episode of rejection; one dose.
 - Transplant recipients at high risk for cytomegalovirus infections (CMV) or for treatment of CMV pneumonitis in combination with antiviral therapy: Continued treatment may be considered if the member demonstrates a need for continued prophylaxis. Prescriber submit documentation for Medical Director Review.
- Duration of continuation of treatment: May be authorized up to **THREE (3) months** at a time.

3. Route of Administration [ALL]

- Intravenous Immune Globulin (IVIg) is considered **provider-administered**
- Site of administration (in a hospital, hospital outpatient, community office or home-based setting) will be determined by the Plan, in consultation with the requesting physician to be the most clinically appropriate and/or medically necessary and must be based upon clinical and individual condition, in order to minimize risk to the patient (i.e. co-morbid conditions, patient’s ability to administer IgG at home, compliance, and availability and ease of IV access)
- IVIg products are not interchangeable. Any changes of IVIg product brand should be provided under physician supervision in a facility equipped to handle the most severe acute medical complications whenever feasible.
- If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.
- Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

COVERAGE EXCLUSIONS

Intravenous Immune Globulin (IVIg) is considered **experimental and investigational** for all other indications not addressed in the ‘Recommendations/Coverage Criteria.’ Diagnoses which are unproven and/or do not support a conclusion concerning the health outcomes or benefits associated with this procedure. Therefore, all other uses of Intravenous Immune Globulin (IVIg) that are not an FDA-approved indication or included in ‘Coverage Criteria’ section above are considered experimental/investigational and is not a covered benefit.

- Organ Transplant Rejection
 - ◆ *One randomized controlled trial and one non-randomized, retrospective, observational study were identified describing the clinical effectiveness of off-label use of IVIg for the treatment of solid organ transplant rejection. Evidence of moderate quality from one randomized controlled trial investigating IVIg combined with rituximab versus placebo in 25 renal transplant patients with chronic antibody mediated rejection indicated that there was no important effect on renal function.*

Evidence of limited quality from one non-randomized, retrospective observational study investigating IVIg versus methylprednisolone in 39 renal transplant patients with antibody mediated rejection indicated that there was a significant improvement in renal function. Further evidence from larger, long-term studies, including investigating other types of organ transplants, is necessary to reduce uncertainty. (Khangura SD, et al. 2018)

- ❑ IVIg and Rituxan (Rituximab) for desensitization **prior** to renal transplantation
 - ◆ *The combination of IVIg and Rituxan (Rituximab) for desensitization prior to renal transplantation is investigational at this time. Larger, prospective, randomized controlled trials are required to evaluate the long-term efficacy and safety of this treatment and to compare this protocol with the current treatment of IVIg alone.*

- ❑ Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation. Refer to 'Summary of Evidence' section for additional information.
EXCEPTION: Medical Director may consider authorization if prescribed by, or in consultation with, a physician affiliated with a transplant center. Additional documentation and discussion with Prescriber, as deemed necessary by Molina Medical Director, may be required.
 - ◆ *There is insufficient evidence to recommend for, or against, the use of IVIg for desensitization for patients undergoing heart, lung, or liver transplantation.^A*

BACKGROUND/SUMMARY

Immune globulin therapy is derived from the pooled plasma of thousands of donors and contains primarily (>98 %) human immunoglobulin G (IgG) with trace amounts of IgA and IgM. The products differ by route of administration [intravenous (IV) or subcutaneous (SC)], specific titers of each IgG subclass, viral inactivation processes, and additives such as sucrose and sodium. While all immune globulins have comparable efficacy in the treatment of immune deficiencies, the products are not interchangeable. **Selection of product should take into consideration various patient factors including diagnosis, condition and severity, individual comorbidities, available alternative treatments, and previous response to intravenous immune globulin therapy.**

Antibody-Mediated Rejection

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, ABMR).

- ABMR is the most common cause of allograft failure after kidney transplantation. Increasing evidence suggests that the prevention and treatment of antibody-mediated injury requires a combination of strategies to inhibit B cell development, maturation, and activity. Despite a relatively large number of observational studies, it is not clear which combination therapy is the safest and most effective (Djamali A.).
- Acute humoral rejection (AHR) is also an ABMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIg, pheresis or a combination of modalities.
- To date, plasmapheresis together with the application of intravenous immunoglobulins IVIg has been the mainstay of ABMR treatment [4, 5].
- Pre-treatment with IVIg (desensitization) may reduce the risk of ABMR in highly sensitized renal transplant patients.

Reference:

- Kälble T, Alcaraz A, et al. *Guidelines on renal transplantation. Arnhem, The Netherlands: European Association of Urology (EAU); 2009 Mar. [cited March 21, 2013]; Available from: http://www.uroweb.org/fileadmin/tx_eauguidelines/2009/Full/Renal_Transplant.pdf*
- Jordan SC, et al. *Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol 2004 15:3256-62.*

LUNG TRANSPLANT

Lung transplant recipients carry the highest risks of infection among all the solid organ transplant patients, especially within the first year post-transplant when level of immunosuppression is often highest (Florescu DF, et al. 2013). HGG is defined as serum IgG < 700 mg/dL and is observed frequently in lung transplant patients. HGG, especially severe HGG (IgG < 400 mg/dL) has been associated with increased risks of infection, mortality, and rejection.

IVIg replacement with non-specific IVIG or CMV-Ig may have some positive effects on infection, although its effects on mortality and rejection are conflicting and requires further elucidation. Based on the existing data, routine IgG level monitoring is reasonable before and after lung transplant. Replacement with IVIg should be considered, especially in patients with severe HGG (IgG < 400 mg/dL) and native and/or donor infections. The benefits of replacement must be weighed against the potential adverse effects and cost of IVIg. Further larger, prospective studies are needed to determine the effects of IVIG replacement on infection, rejection, and mortality.

RENAL TRANSPLANT

- ⌘ The optimal treatment of active ABMR is unclear, and there have been no randomized, controlled trials with adequate statistical power to compare the safety and efficacy of different therapeutic strategies (Velidedeoglu E, et al. Summary of 2017 FDA Public Workshop: Antibody-mediated Rejection in Kidney Transplantation) [Djamali A. 2019].
- ⌘ KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009): Recommendations for the treatment of ABMR are primarily based upon available, low-quality evidence and are largely consistent with the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines
- ⌘ Jordan et al. (2004) reported outcomes of a randomized, double-blind, placebo-controlled clinical trial for the reduction of anti-HLA antibody levels and improvement of transplant rates with IVIg.

- A total of 101 participants with end stage renal disease (ESRD) and highly sensitized to HLA antigens (panel reactive antibody [PRA] greater than or equal to 50% monthly for 3 months) were enrolled in a National Institutes of Health (NIH) sponsored trial (IG02).²
- Participants received either IVIg 2 gm/kg monthly for 4 months or an equivalent volume of placebo with additional infusions at 12 and 24 months after entry, if not transplanted.
- If transplanted, additional infusions were given monthly for 4 months.
- Baseline PRA levels were similar in both groups. However, IVIg significantly reduced PRA levels in the IVIg group compared with placebo. Sixteen IVIg participants (35%) and 8 placebo participants (17%) were transplanted.
- Result: Rejection episodes occurred in 9 of 17 IVIg and 1 of 10 placebo subjects. Seven graft failures occurred (4 IVIg; 3 placebo) among adherent participants with similar 2-year graft survival rates (80% IVIg; 75% placebo). With a median follow-up of 2 years after transplant, the viable transplants functioned normally.
- It was concluded that IVIg is better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized individuals with ESRD. Transplant rates for highly sensitized patients with ESRD awaiting kidney transplants are improved with IVIG therapy.

Reference: Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol. 2004; 15(12):3256-3262.

CARDIAC TRANSPLANT

IVIg is commonly used to treat the highly sensitized patient awaiting cardiac transplantation; however, it has never been systematically studied after transplantation to prophylactically reduce the incidence of AMR (Colvin MM; AHA 2015). When used for the management of AMR or in desensitization protocols, IVIg is frequently used in combination with other immune therapies. Very few data have been reported that support the use of IVIg for the treatment of acute AMR. In a study of 7 kidney and 3 heart transplant recipients with AMR, IVIg administered in combination with cyclophosphamide or tacrolimus was reported to reverse rejection in all patients within 2 to 5 days of infusion. The incidence of recurrence, however, was high (Jordan SC, et al. 1998). Similar findings have been reported in other small series.³⁸

- ⌘ Kobashigawa et al. (2009) reported recommendations from an international consensus conference addressing those who are sensitized and awaiting heart transplant. The 71-member panel examined diagnostic and treatment regimens from transplant centers and reached consensus for anti-HLA antibody screening and testing methodology. The desensitization recommendations pre-transplant included IVIg, plasmapheresis, and possibly rituximab.

Reference: Kobashigawa J, Mehra M, West L, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant. 2009; 28(3):213-225.

- ⌘ Kobashigawa and colleagues (2011) reported recommendations from an international consensus conference addressing antibody mediated rejection (ABMR) in heart transplantation. The conference participants noted that the problem of ABMR is due to the many different features of ABMR making the current methods for diagnosis and treatment difficult. The panel examined diagnostic and treatment regimens from transplant centers and the published literature. Regarding the use of IVIg, initial treatment for ABMR may include high dose corticosteroids, plasmapheresis and IVIg.

Reference: Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011; 30(3):252-269.

⌘ Jordan et al. (2011), in a review, addressed clinical applications of Ig in solid organ transplantation and suggested that IVIg has a much broader ability to regulate cellular immunity and is a modifier of complement activation and injury.

- Published clinical data addresses the use of IVIg in desensitization and treatment of antibody-mediated rejection (ABMR) and are supportive for use in kidney transplant recipients, however no clinical trials using IVIg in sensitized individuals have been performed.
- The available data regarding the use of IVIg for desensitization and treatment of ABMR in cardiac and lung allograft recipients is not conclusive.
- The authors noted out that desensitization (immunomodulation) pre- and post-solid organ transplantation requires a coordinated approach so that ABMR and infectious complications are minimized.
- There are currently no FDA approved drugs/protocols for desensitization.

Reference: Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011; 11(2):196-202

DESENSITIZATION THERAPY

Prior to and Immediately after Solid Organ Transplantation

⌘ Renal

Desensitization: The only randomized controlled trial (RCT) to date on desensitizing patients awaiting kidney transplantation found that intravenous immunoglobulin (IVIg) was better than placebo in reducing allosensitization in highly sensitized patients with end stage kidney disease (followed for two years after transplant), and that transplant rates were improved with IVIg therapy (Jordan et al 2004). Non-randomized clinical observational studies suggest that a combination of plasmapheresis and low-dose IVIg is effective and provides a survival benefit for recipients (Montgomery 2011).

IVIg has been used in highly sensitized patients to reduce allosensitization, ischemiareperfusion injuries, and acute rejections episodes in renal allograft recipients. IVIg has been used alone or after plasmapheresis. In one Phase III double-blind trial in patients with end stage renal disease (ESRD), IVIg was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients.

Reference:

- Marfo K, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol.* 2011;6:922-936.
- Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. *J Am Soc Nephrol.* 2004;15:3256-3262.
- Jordan SC, Vo AA, Peng A, et al. Intravenous gammaglobulin (IVIg): a novel approach to improve transplant rates and outcomes in highly HLA-sensitized patients. *Am J Transplant.* 2006;6:459-466.
- Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. *Transfus Med.* 2010;24(1 Suppl 1):S7-S27.
- Jordan SC, Toyoda M, and Kahwaji J. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. *Am J Transplant.* 2011;11:196-202.

⌘ Cardiac

IVIg has been used as a desensitization agent in patients undergoing cardiac transplantation. However, randomized trials are not available and many of the studies have not defined response. The studies have not shown that IVIg alone reduced antibody and results concerning survival after transplant are conflicting.

Reference:

- Shehata N, Palda VA, Meyer RM, et al. *The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med. 2010;24(1 Suppl 1):S7-S27.*
- Jordan SC, Toyoda M, and Kahwaji J. *Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011;11:196-202.*

⌘ **Lung or Liver**

To date, there is no approved therapeutic protocol or consensus on the management of sensitized patients and anti-HLA antibodies before solid organ transplantation. The data are even scarcer regarding thoracic organ transplantation.

⌘ The National Advisory Committee on Blood and Blood Products and Canadian Blood Services in 2010 issued a guideline on the use of IVIg for solid organ transplantation; a panel of experts reviewed findings from a systematic review of evidence. In their literature search, they identified 3 RCTs, all on **kidney transplant**, and numerous observational studies or case series on several types of organ transplantation. Notable recommendations of the panel are as follows:

- When kidney transplantation involves use of a living donor, IVIg is recommended to decrease **donor-specific sensitization**.
- There is insufficient evidence to recommend for, or against, the use of IVIg for **ABO-incompatible** kidney transplantation
- To reduce the risk of **acute antibody-mediated rejection**, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies
- IVIg is recommended after **plasmapheresis** for patients who have received a living donor or deceased kidney donor transplant and who have acute antibody-mediated rejection.
- Consider IVIg when patients have **corticosteroid-resistant rejection**, when other therapies are deemed unacceptable or ineffective.

The following recommendations were issued regarding **non-kidney** solid organ transplantation:

- There is insufficient evidence to recommend for, or against, the use of IVIg for **desensitization** for patients undergoing heart, lung, or liver transplantation.
- There is insufficient evidence to recommend for, or against, the routine use of IVIg for desensitization for patients undergoing heart transplantation to improve graft/overall survival or to treat rejection; however, other factors may influence decision-making.
- There is insufficient evidence to make a recommendation for or against the routine use of IVIg for desensitization for patients undergoing lung transplantation, or for the treatment of rejection; however, other factors may influence decision-making.
- There is insufficient evidence to make a recommendation for, or against the routine use of IVIg for patients undergoing liver transplantation, or for the treatment of rejection/ABO-incompatible liver transplantation.

The Committee further indicated:

- There is limited methodologically rigorous evidence for the use of IVIg for solid organ transplantation.

- Future studies are needed to delineate the effect of IVIg on desensitization using standardized methods for desensitization; the effect of IVIg on acute rejection rates, graft survival, and overall survival; the use of the combined modality IVIg and PP compared either to PP or IVIg alone; and the optimum dosage of IVIg (Shehata, 2010).

References:

- Shehata N, Palda VA, Meyer RM, et al. *The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med.* 2010;24(1 Suppl 1):S7-S27.
- Jordan SC, Toyoda M, and Kahwaji J. *Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant.* 2011;11:196-202.
- Kotton CN, Kumar D, Caliendo AM, et al. *The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation* 2018; 102:900.

⌘ Small Intestine

Limited published information is available in sensitized recipients of small intestine transplants. In a pilot study, highly sensitized patients (n = 6) with intestinal failure (short gut syndrome) who were awaiting isolated small bowel transplant received IVIG and immunosuppressive therapy pre-transplant. Four of the six patients had reduction in high panel peak reactive antibody (PRA) and received intestinal transplantation. Patients continued on IVIG post-transplant at Days 1, 7 and 21. The waiting time for transplant and mortality was similar to non-sensitized patients. IVIG is also used post-transplant to treat acute antibody-mediated rejection and steroid-resistant acute cellular rejection. These patients are hospitalized.

Reference:

- Gondolesi G, Blondeau B, Maurette R, et al. *Pretransplant immunomodulation of highly sensitized small bowel transplant candidates with intravenous immune globulin. Transplantation.* 2006;81:1743-1746.
- Hawksorth JS, Rosen-Bronson S, Island E, et al. *Successful isolated intestinal transplantation in sensitized recipients with the use of virtual crossmatching. Am J Transplant.* 2012;12 Suppl 4:s33-s42.

OTHER BACTERIAL OR VIRAL INFECTIONS

IVIg has been used alone or in conjunction with appropriate anti-infective therapy to prevent or modify acute bacterial or viral infections (e.g., cytomegalovirus infections) in patients with iatrogenically induced or disease-associated immunosuppression such as patients undergoing major surgery (e.g., cardiac transplants) or patients with hematologic malignancies, extensive burns, or collagen-vascular diseases (AHFS 2019; Immune Globulin).

Cytomegalovirus (CMV) is one of the most common opportunistic infections that affect the outcome of solid organ transplantation. The updated guideline from the American Society of Transplantation Infectious Diseases Community of Practice provides evidence-based and expert recommendations for screening, diagnosis, prevention, and treatment of CMV in solid organ transplant recipients.

CMV Infections, Prophylaxis or Treatment in Solid Organ Transplantation:

- Antiviral prophylaxis and preemptive therapy are the mainstays of CMV prevention. Valganciclovir and intravenous ganciclovir remain as drugs of choice for CMV management.
- Antiviral agents (Valganciclovir and intravenous ganciclovir) and Cytogam are effective in preventing and treating CMV in solid organ transplant recipients.

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation (2018) (Kotton, CN)

- 6 to 12 months of prophylaxis for CMV Donor(+)/Recipient (-) lung transplant recipients (Kotton, CN 2019).
- For CMV D+/R+ and D-/R+ lung transplant recipients, a minimum of six months of prophylaxis is recommended.
- The decision on prophylaxis duration of prophylaxis depends upon several factors, including the patient's risk of CMV reactivation, development of drug toxicity, and the feasibility of frequent viral load monitoring.

Reference:

- Preiksaitis JK, Brennan DC, Fishman J, et al. Canadian Society of Transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. *Am J Transplant.* 2005;5:218-227.
- Pereyra F, Rubin RH. Prevention and treatment of cytomegalovirus infection in solid organ transplant recipients. *Curr Opin Infect Dis.* 2004;17:357-361.
- Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. *Transfus Med.* 2010;24(1 Suppl 1):S7-S27.

Points for consideration:

- Oral valganciclovir and intravenous ganciclovir are the drugs of choice for CMV prophylaxis. Valganciclovir is the drug of choice for the prophylactic management of CMV infection after lung transplantation and has proven efficacy in heart, kidney, and kidney-pancreas transplantation compared with oral ganciclovir (Zamora, 2019).
- Valganciclovir prophylaxis is preferred over pre-emptive therapy for patients who are seropositive for CMV or who received an organ from a seropositive donor who are receiving antilymphocyte antibodies, high doses of glucocorticoids, or other potent immunosuppressive used for the treatment of rejection, since such patients are at increased risk of CMV infection. Prophylaxis should be continued for one to three months after the antirejection therapy has been completed (Zamora, 2019).
- The approach to prophylaxis chosen for each patient depends upon protocols developed at each transplant center.
- The relative efficacy and safety of CMV-IGIV and IGIV for the prevention of CMV disease in solid organ transplant recipients or allogeneic BMT patients have not been clearly established in prospective, randomized, controlled studies. While it is unclear whether CMV-IGIV offers any therapeutic advantage over IGIV, some clinicians suggest that CMV-IGIV may be preferred if an immune globulin is used for CMV prophylaxis in solid organ transplant recipients since it contains a standardized CMV antibody content that is 4-8 times higher than that contained in IGIV (AHFS 2019; CMV-IGIV).

COMBINATION THERAPY WITH RITUXIMAB

IVIg is one of the most common therapies used to decrease antibody-mediated immunity. IVIg causes B cell apoptosis, reduces B cell numbers, and down-regulates several B cell surface antigens. It also blocks binding of donor-reactive antibodies and may inhibit complement activation. It has a relatively low side effect profile. The combination of IVIg and rituximab has also been used in the setting of organ transplantation. IVIg ± rituximab has been administered to highly human leucocyte antigen (HLA)-sensitized patients to reduce anti-HLA antibody levels, allowing transplantation in these patients. IVIg in combination with rituximab is also used in the treatment of antibody-mediated rejection following transplantation.

- ⌘ Vo et al reported on 20 highly sensitized patients who received 2 g/kg of IVIg on days 0 and 30. Mean panel reactive antibodies (PRAs) were $77\% \pm 19\%$. Rituximab was given at days 7 and 22. Sixteen patients were offered a kidney transplant within a mean time of 5 ± 6 months (range, 2-18 months). Graft survival and patient survival were 94% and 100%, respectively, and the rejection rate was 50%. The researchers concluded that the combination of IVIg and rituximab was effective as a desensitization regimen, but they acknowledged the need for larger trials to evaluate the efficacy of this intervention (Vo AA, et al. 2008).
- ⌘ In 2010, Vo and colleagues reported on 76 HLA-sensitized individuals who were treated with IVIg and rituximab prior to kidney transplantation during 2006 and 2009.⁴ The study examined the efficacy of IVIg and rituximab on the reduction of anti-HLA antibodies that led to kidney transplantation with incurring the risk of ABMR and immediate graft loss. All participants were deemed high immunologic risks with PRA 30% - 79% in 25% of individuals and 75% of the participants had PRA $\geq 80\%$. Thirty-one individuals received living donor (LD) and 45 individuals received deceased donor (DD) kidney transplants. Recipients of deceased donor kidneys had a mean waiting list time of 95 ± 46 months prior to desensitization but received transplants within 4 months after receiving combination treatment with IVIG and rituximab. Acute rejection (AR) occurred in 37% of participants (8% cell mediated rejection [CMR] and 29% ABMR). Nine individuals had graft losses, with ABMR involved in 6 cases. Recipient and allograft survivals were 95% and 84%, respectively. The authors concluded, "*IVIG and rituximab seems to offer significant benefits in reduction of anti-HLA antibodies, allowing improved rates of transplantation for highly sensitized patients, especially those awaiting DD, with acceptable antibody-mediated rejection and survival rates at 24 months*" (Vo, 2010). Additional analysis in a randomized trial was recommended.
- ⌘ Rituximab is recommended for antibody mediated rejection (AbMR) in heart transplant recipients, with steroids, plasmapheresis and/or IVIG, to reduce the risk of recurrent rejection (Costanzo et al, 2010).
 - Initial therapy of AbMR can include immunoadsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid.
 - The guidelines state that rituximab can be added to reduce the risk of recurrent rejection. Changes in therapy, which can be considered for maintenance immunosuppression in patients who experience antibody mediated rejection, can include switch to tacrolimus in patients receiving cyclosporine-based immunosuppression, increased doses of mycophenolate mofetil, and corticosteroids.
- ⌘ Macklin et al (2017) conducted a systematic review to evaluate the evidence for use of rituximab in the treatment of acute and chronic antibody-mediated renal transplant rejection (AAMR; CAMR): A systematic search of four databases and three trial registries was conducted. The small number and heterogeneous nature of included studies precluded meta-analysis and thus a narrative review was conducted. A total of 28 records met the inclusion criteria (AAMR, 18 records relating to 9 studies; CAMR, 10 records relating to 7 studies). Two systematic reviews were identified that had differing inclusion criteria to this current review. Of seven primary studies in the setting of AAMR, four reported increased graft survival and one reported improved graft function with rituximab. This contrasts with CAMR in which only one of seven studies reported improved graft outcomes with a rituximab-based regimen; three studies reported inferior outcomes and three reported no difference. Only one study reported that rituximab was associated with an increase in adverse effects. The included studies suggest that rituximab may be of some benefit in the setting of AAMR but a lack of high-quality evidence precludes firm conclusions from being drawn. Rituximab does not appear to reliably improve outcomes in CAMR. **It was concluded that well-conducted studies are required to better define the effects and long-term safety profile of rituximab in the treatment of antibody-mediated renal transplant rejection** (Macklin 2017).

Reference:

- *Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242–251.*
- *Vo AA, Peng A, Toyoda M, et al. Use of intravenous immune globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney transplantation. Transplantation. 2010; 89(9):1095-1102.*
- *Macklin PS, Morris PJ, Knight SR. A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection. Transplant Rev (Orlando). 2017;31(2):87-95.*

DEFINITIONS

N/A

APPENDIX

Appendix 1: Comparative intravenous immune globulin (IVIg) preparations

Brand Name	Supplied As	IgA Content	Osmolality	Excipient Information	Filtration Requirements	Additional Notes
Bivigam	10% (liquid); 50 mL and 100 mL	≤ 200 mcg/mL	510 mOsm/kg	Glycine, polysorbate 80, NaCl	None	N/A
Carimune NF	3%, 6%, 9%, 12% (lyophilized); 3 g, 6 g, and 12 g	1,000-2,000 mcg/mL	192-1,074 mOsm/kg	Sucrose, NaCl	None	Osmolality varies based on concentration and diluent
Flebogamma DIF	5%, 10% (liquid); 5%: 10 mL, 50 mL, 100 mL, 200 mL, 400 mL; 10%: 50 mL, 100 mL, 200 mL	< 50 mcg/mL (5%); < 32 mcg/mL (10%)	240-370 mOsm/kg	Sorbitol, polyethylene glycol	None	N/A
Gammagard	10% (liquid); 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL	37 mcg/mL	240-300 mOsm/kg	Glycine	In-line filter optional	N/A
Gammagard S/D	5%, 10% (lyophilized); 2.5 g, 5 g, 10 g	≤ 2.2 mcg/mL or < 1	636 mOsm/L (5%)	Glycine, dextrose, albumin, polyethylene glycol, octoxynol-9,	Supplied with 15 micron filter	2 low-IgA formulations available

		mcg/mL for 5%		polysorbate 80, tributyl phosphate		
Gammaked	10% (liquid); 10 mL, 25 mL, 50 mL, 100 mL, 200 mL	46 mcg/mL	258 mOsm/kg	Glycine, caprylate	None	N/A
Gammaplex	5% (liquid); 50 mL, 100 mL, 200 mL, 400 mL	< 10 mcg/mL	420-500 mOsm/kg	Glycine, polysorbate 80, sorbitol, NaCl, sodium acetate	None	Contraindicated if hereditary intolerance to fructose and in infants and neonates for whom sucrose or fructose intolerance has not been established
Gamunex-C	10% (liquid); 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 400 mL	46 mcg/mL	258 mOsm/kg	Glycine, caprylate	None	N/A
Octagam	5%, 10% (liquid); 5%: 20 mL, 50 mL, 100 mL, 200 mL, 500 mL; 10%: 20 mL, 50 mL, 100 mL, 200 mL	5%: ≤ 200 mcg/mL; 10%: 106 mcg/mL	310-380 mOsm/kg	Maltose, triton X-100, tributyl phosphate	In-line filter optional (0.2-200 microns)	Contraindicated if corn allergy; may falsely elevate glucose levels
Panzyga	10% (liquid): 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL	100 mcg/mL (average)	240-310 mOsm/kg	Glycine	Use in-line filter (0.2-200 microns)	Contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity
Privigen	10% (liquid); 50 mL, 100 mL, 200 mL, 400 mL	≤ 25 mcg/mL	240-440 mOsm/kg	L-proline, albumin	None	Contraindicated in patients with hyperprolinemia

Abbreviation: IgA, immunoglobulin A; N/A, not applicable.

Reference: Table above adapted from Dynamed Plu. Ipswich (MA): EBSCO Information Services. 1995 - Record No. T915089, Comparative intravenous immune globulin (IVIg) preparations; [updated 2018 Dec 04, cited May 2020]. Available from <https://www.dynamed.com/topics/dmp~AN~T915089>. Registration and login required.

APPENDIX 2: Cytomegalovirus Intravenous Immune Globulin (CMV-IG; Cytogam®)

FDA-Approved Indication:

Cytomegalovirus prophylaxis: For the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

FDA-Approved Dosing and Administration

Time frame after transplant	Kidney transplant	Liver, lung, pancreas, heart
Within 72 hours of transplant	150 mg IG/kg	150 mg IG/kg
Weeks 2,4,6,8 post-transplant	100 mg IG/kg	150 mg IG/kg
Weeks 12 & 16 post-transplant	50 mg IG/kg	100 mg IG/kg

*Maximum recommended total dosage per infusion is 150 mg IG/kg; max rate: 60mg/kg/hr

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
90283	Immune globulin (IgIV), human, for intravenous use

HCPCS	Description
J1459	Injection, immune globulin (PrIVIgen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (Vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous lyophilized (e.g., powder), 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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Package Insert, FDA, Drug Compendia

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- Bivigam (immune globulin intravenous [human]) [prescribing information]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; January 2017.
- Carimune NF (immune globulin intravenous [human]) [prescribing information]. Kankakee, IL: CSL Behring LLC; November 2016.
- Cutaquig (immune globulin subcutaneous human) [prescribing information]. New York, NY: Pfizer Labs; November 2020.
- Cuvitru (immune globulin subcutaneous [human]) [prescribing information]. Lexington, MA: Baxalta US Inc; May 2019.
- Cytogam (cytomegalovirus immune globulin intravenous [human]) [prescribing information]. Kankakee, IL: CSL Behring; May 2018.
- Flebogamma 5% DIF (immune globulin intravenous [human]) [prescribing information]. Barcelona, Spain: Instituto Grifols, SA; July 2017.
- Flebogamma 10% DIF (immune globulin intravenous [human]) [prescribing information]. Barcelona, Spain: Instituto Grifols; January 2016.
- Gammagard Liquid (immune globulin intravenous and subcutaneous [human]) [prescribing information]. Lexington, MA: Baxalta US Inc; July 2017.
- Gammagard S/D (immune globulin intravenous [human]) [prescribing information]. Westlake Village, CA: Baxalta US Inc; March 2017.

- Gammaked (immune globulin intravenous and subcutaneous [human]) [prescribing information]. Fort Lee, NJ: Kedrion Biopharma Inc; June 2018.
- Gammaplex 5% (immune globulin intravenous [human]) [prescribing information]. Durham, NC: BPL, Inc; September 2019.
- Gammaplex 10% (immune globulin intravenous [human]) [prescribing information]. Durham, NC: BPL; received January 2019.
- GamaSTAN (immune globulin intramuscular [human]) [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics Inc; February 2018.
- Gamunex-C (immune globulin [human]) [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics LLC; June 2018.
- Hizentra (immune globulin) [prescribing information]. Kankakee, IL: CSL Behring LLC; March 2018.
- HyQvia (immune globulin infusion 10% [human] with recombinant human hyaluronidase) [prescribing information]. Lexington, MA: Baxalta US Inc; January 2019.
- Octagam 5% (immune globulin intravenous [human]) [prescribing information]. Hoboken, NJ: Octapharma USA; January 2019.
- Octagam 10% (immune globulin intravenous [human]) [prescribing information]. Hoboken, NJ: Octapharma USA; April 2015.
- Panzyga (immune globulin intravenous [human]) [prescribing information]. Hoboken, NJ: Octapharma USA; August 2018.
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Policy History	Approval Date
<u>Policy Developed</u> Peer Review. AMR Tracking Num: 547462. 1/28/2015 Board certified in Surgery General, Surgery Transplant.	MCP 2/2/2015
<u>Revision*</u> Peer Review. AMR Tracking Num: 1142945. 8/5/2019. Board certified in Surgical Critical Care, Surgery Vascular, Surgery General, Surgery Transplant.	P&T Q3 2019
<u>Annual Review*</u> No coverage criteria changes or notable revisions with this annual review. Minor update however no change to intent: Added 'Drug Shortage' section	P&T Q3 2020
<u>Revision*</u> Peer Review. AMR Tracking Num: 1262086. 9/21/2020. Board certified in Oncology, Hematology	Q4 2020

*NOTE: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.