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 Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of immune globulin products FDA-approved for subcutaneous infusion (SC Ig) for the treatment of primary immune deficiency when appropriate criteria are met with consideration for members in whom IVIg has failed, is not tolerated, and contraindicated or for members already stable on a SC Ig product:

- **Gammagard® Liquid 10%**
  
  Gammagard® Liquid 10% is administered by IV infusion. Alternatively, Gammagard® Liquid 10% may be administered by subcutaneous infusion for the treatment of primary humoral immunodeficiency

- **Gammaked™ 10%**
  
  Administer IV for treatment of primary humoral immunodeficiency, ITP, and CIDP; may also be administered subcutaneously for the treatment of primary humoral immunodeficiency.

- **Gamunex®-C 10%**
  
  Gamunex®-C 10% is administered by IV infusion. Alternatively, Gamunex®-C 10% may be administered by subcutaneous infusion for the treatment of primary humoral immunodeficiency

- **Hizentra® 20%**

- **HyQvia® 10%**
  
  Hizentra® and HyQvia® are formulated only for SC use and cannot be given IV.

The intent of this coverage policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. In absence of a product listed below and in addition to applicable criteria outlined within the drug policy, prescribing and dosing information from the package insert is the clinical information used to determine benefit coverage.

- Refer to MCP-043 for Intravenous Immune Globulin (IVIg) drug products.

- Applications of this product for conditions other than primary immunodeficiencies are considered OFF-LABEL in the United States and are not addressed in this policy.
Abbreviations:

- **Immune globulin, intravenous (human)** will be 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** will be abbreviated as subcutaneous immune globulin (SCIG).

### SUBCUTANEOUS INFUSION IMMUNE GLOBULIN

- Immune globulin subcutaneous (SCIG) is a protein solution that contains at least 98% immunoglobulin G (IgG). It is used in the treatment of primary immunoglobulin deficiency. Lifelong replacement therapy with human immune globulin provides passive immunity to decrease susceptibility to life-threatening infections in patients with predominant antibody deficiencies. C,d [Clinical Pharmacology, 2016]

- There are three ways to administer immune globulin subcutaneously. These differ in both the frequency of administration and how the SCIG is given. The first uses infusion pumps to give predominantly weekly infusions (called "traditional" in this review). The second, termed "rapid-push SC," is given using only a syringe and butterfly needle at frequencies from several times per week to daily. The third is hyaluronidase-facilitated SCIG (fSCIG), generally given every three to four weeks. ¹,³,⁴

- SCIG has a lower bioavailability than IVIG, so must be given in higher doses to achieve the same serum IgG concentrations. However, subcutaneous delivery may result in higher steady-state IgG levels due to less variation in IgG levels.

- Comparison of SCIG approved products a-e
  - Hyqvia® is also an immune globulin product for subcutaneous use, approved for patients with PID, and is available as a 10% solution for every three to four week subcutaneous infusion.
  - Gammaked®, Gamunex-C®, and Gammagard Liquid® are approved for both intravenous and subcutaneous use for treatment of PID. Gammagard Liquid, Gammaked and Gamunex-C, when administered subcutaneously, are FDA-approved for the treatment of primary immunodeficiency syndromes only. All three are available as a 10% solution.
  - Hyqvia 10% is formulated with hyaluronidase, to allow for larger volume infusion at a single injection site. Up to 600 mL (60 grams) may be given per injection site (for patients > 40 kg) at an infusion rate up to 300 mL/hour. The recommended maximum dose per injection site for Hizentra 20% is 25 mL (5 grams), given over a maximum of 25 mL/hour.
  - Multiple injection sites (three to four) are necessary for weekly infusion (Hizentra, Gammaked, Gamunex-C, Gammagard) for an average patient because of the volume that must be infused, whereas Hyqvia may be infused monthly.
  - None of these products have been approved for SC administration for any other indications, other than PID. Because other diagnoses usually require larger doses (based on grams per kilogram) with a high volume per dose, subcutaneous administration is generally not feasible.
  - Injection site swelling, redness, and itching were reported in the majority of patients.

- A position statement from the American Academy of Asthma, Allergy and Immunology (Orange, et al., 2005)⁵ states that "the decision to administer IVIg to patients with primary deficiencies in antibody production should be based on: 1) abnormalities of serum immunoglobulin concentrations; 2) clinical history of infections; and, when appropriate, 3) the demonstrated inability to produce antibody normally following antigenic stimulation."

  Guidelines from the American Academy of Asthma, Allergy & Immunology (Orange, et al., 2006) state; "Reduced levels of serum immunoglobulin in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (i.e., patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both) is a clear indication for IgG replacement."

- **Similar clinical efficacy of SCIG replacement therapy versus IVIg**
Subcutaneous and intravenous immune globulin are similarly effective at preventing infections.

- In 2013, Lingman-Framme and Fasth published a systematic review of the literature on SCIg compared with IVIg for treatment of primary and secondary immunodeficiencies. The authors identified 20 studies; 2 were RCTs, and 19 included patients with primary immunodeficiencies. The primary outcome of interest was the number of serious bacterial infections, defined as bacterial pneumonia, meningitis, osteomyelitis, sepsis, and peritonitis. Only 3 studies reported on serious bacterial infections during both SCIg and IVIg administration, and no serious bacterial infections were identified. Five studies reported the annual number of infections (bacterial and/or viral), and no significant difference was found in infection rates associated with SCIg and IVIg. Four of these studies found that patients reported a better quality of life with home-based SCIg compared with hospital-based IVIg. Moreover, all 11 studies that reported IgG trough levels found higher levels with SCIg compared with IVIg.

- The similar clinical efficacy of SCIg replacement therapy versus IVIg, in the context of more favorable pharmacokinetic parameters and a simpler delivery method for chronic therapy, suggests SCIg treatment may be considered medically necessary in the place of IVIg to prevent recurrent infections in patients with primary immunodeficiencies PID who require lifelong immunoglobulin replacement therapy.

- Viviglobin was discontinued by the manufacturer in 2013; it is likely that findings of the studies conducted with Viviglobin generalize to other SCIg products.

### 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.

### Primary Immunodeficiency Diseases

IgIV is used for replacement therapy in patients with primary humoral immunodeficiency who are unable to produce sufficient amounts of IgG antibodies. IgIV has been used to promote passive immunity in patients with congenital agammaglobulinemia, common variable hypogammaglobulinemia, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.a-g

- **Hizentra®** is an immune globulin product for subcutaneous use, approved for patients with primary immune deficiency (PID). Available as: 20% solution for weekly subcutaneous infusion.

- **Hyqvia®** is also an immune globulin product for subcutaneous use, approved for patients with PID, and is available as a 10% solution for every three to four week subcutaneous infusion.b

- **Gammaked®, Gamunex-C®, and Gammagard liquid®** are approved for both intravenous and subcutaneous use for treatment of PID. All three are available as a 10% solution.

FDA approval:

- 2003: Approval of both Gamunex-C® and Gammaked® immune globulin intravenous (IVIg) (human) 10% liquid products for the treatment of serious infections in individuals with PIDD via IV or SC administration.

- 2005: Gammagard Liquid® IVIg (human) 10% liquid product for the treatment of PIDD via IV or SC administration.

- March 2010: A ready-to-use 20% liquid formulation (Hizentra) for weekly SC replacement therapy in patients with primary immunodeficiencies

- September 2013: Hizentra was approved for biweekly (once every 2 weeks) administration.
January 2015: Hizentra was approved for more frequent dosing, with administration possible up to 7 times per week.

**FDA-APPROVED PRODUCTS AND INDICATIONS**

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*Primary immunodeficiency diseases (PID), idiopathic thrombocytopenic purpura (ITP), B-cell chronic lymphocytic leukemia (CLL), chronic inflammatory demyelinating polyneuropathy (CIDP), Kawasaki disease and/or multifocal motor neuropathy (MMN).*

- 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 primary immunodeficiency disease (PID).**
  - All conditions are FDA approved for the intravenous (IV) route.
  - IVIG products will not be approved 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).a-e
- All Ig products (IVlg and SCIg) are FDA approved for the indication of PID. However, only PIDa-e is FDA-approved for the subcutaneous route (SC).

**Black Box Warnings**

*Thrombosis: Thrombosis may occur. 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 immune globulin 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.a-e*

**CLASSIFICATION:** Immunoglobulins
SUMMARY OF EVIDENCE/POSITION

SClG Therapy

- There are no head-to-head studies comparing concentrated SClG to IVIg in PID and no evidence-based reviews demonstrating that SClG is more effective than IVIg to improve and maintain immune globulin levels. Therefore, unless contraindicated, a trial of IVIg is required before SClG products will be considered for authorization.

- There is robust evidence to support the use of subcutaneous IgG (SClG) for primary immunodeficiency. The SClG formulation may be appealing to patients due to a lack of requirement of venous access, a perceived sense of independence associated with self-administration, and more consistent serum IgG levels. However, limitations of SClG include increased dosing frequency, requirement of multiple dosing sites, and the need for competent and adherent patients.

- There is no strong evidence that indicates a preferential route of administration of IgG. Systematic reviews indicate that there is no difference in efficacy between IVIg and SClG products. Products with low IgA counts may be preferable to those who experience infusion reactions.

- There is no strong evidence that shows that the differences in the pharmacokinetic profiles of IVIg and SClG translate to meaningful improvements in patient outcomes. While some studies showed a lower incidence of adverse events in SClG versus IVIg, the 20% SCIG formulation has not been directly compared to IVIg.

- 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.

- Molina Healthcare does not cover subcutaneous immune globulin (SClG) for non-FDA approved conditions, including but not limited to conditions when its use is considered investigational or unproven, and is not supported by evidence-based literature.

- Applications of Subcutaneous Immune Globulin (SClG) for conditions other than primary immunodeficiencies are considered not addressed in this policy. Conditions that are off-label may be addressed by Molina Healthcare’s off-label coverage for prescription drugs and biologics policy, Off-Label Use of Drugs and Biologic Agents MCP-162.

PREFERRED Immunoglobulin: IVIg Products

- There is robust evidence to support the use of intravenous immunoglobulin G (IVIg) for primary immunodeficiency. This route of administration allows a large volume per infusion, and is administered relatively infrequently (every three to four weeks), however it must be administered by a trained professional, venous access is required, and it is associated with greater fluctuations in IgG levels, potentially resulting in a greater incidence of adverse effects.

- 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 osmolarity 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.

**RECOMMENDATIONS/COVERAGE CRITERIA**

Subcutaneously administered immunoglobulin (SCIlg) as an alternative to intravenous immunoglobulin therapy may be considered for members who meet ALL of the following criteria [ALL]

1. **Prescriber specialty [ONE]**
   - Prescribed by, or in consultation with, a board-certified immunologist, an infectious diseases physician who treats patients with primary immune deficiencies, or a physician who has specialized expertise in managing patients on immune globulin therapy (e.g., immunologist, hematologist, neurologist, etc.). Submit consultation notes if applicable.
   - **NOTE:** Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.
   - **Clinical Rationale:** Due to the expertise required for evaluation and diagnosis of patients treated with SCIlg, in addition to the monitoring required for adverse events and long-term efficacy, authorization requires SCIlg to be prescribed by or in consultation with a physician who specializes in the condition being treated.D,E

2. **Diagnosis/Indication [ALL]**
   - Clinically documented diagnosis (includes chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis) of:
     - A definitive diagnosis of a **primary humoral immunodeficiency** (list may not be all-inclusive): [ONE]
       - Autosomal recessive agammaglobulinemia
       - Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
       - Combined immunodeficiency disorders
       - Ataxia-telangiectasia
       - DiGeorge syndrome
       - Nijmegan breakage syndrome
       - WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
       - Wiskott Aldrich syndrome
       - Common variable immunodeficiency [CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia]
       - Congenital hypogammaglobulinemia late onset, ICOS impaired
       - Congenital/X-linked agammaglobulinemia (XLA or Bruton’s agammaglobulinemia)
       - Good syndrome (immunodeficiency with thymoma)
       - Hyperimmunoglobulinemia E syndrome
       - Hypogammaglobulinemia
       - ICF syndrome
       - Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
       - Selective IgM deficiency
       - Severe combined immunodeficiency
       - Specific antibody deficiency
       - Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
       - X-linked immunodeficiency with hyperimmunoglobulin M

   - **EXCEPTION**
     - SCIlg may be authorized for members who meet ALL of the following criteria (without meeting additional criteria). Prescriber submit required documentation to Pharmacy/Medical Director for review: [ALL]
 Documentation of risk factors for volume overload (e.g. congestive heart failure, end stage renal disease and renal dysfunction) AND
 Documentation of Prescriber/Physician’s order of fluid volume restriction

 Documentation of ALL of the following criteria for treatment with immune globulin: A) Laboratory evidence of immunoglobulin deficiency, B) Documented inability to mount an adequate immunologic response to inciting antigens, AND C) Persistent and severe infections despite treatment with prophylactic antibiotics [A, B, AND C]

A. Laboratory evidence of immunoglobulin deficiency [ONE]
   Abnormalities of serum immune globulin concentration as indicated by ONE (1) of the following laboratory evidence of the immunoglobulin deficiency: [ONE]
   ☑ Laboratory evidence such as absence of B lymphocytes that supports evidence of immunoglobulin deficiency
   ☑ Common variable immunodeficiency (CVID): total IgG < 400mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions
   ☑ Congenital agammaglobulinemia (X-linked or autosomal recessive): total IgG less than 200 mg/dL
   ☑ Persistent hypogammaglobulinemia: Total IgG less than 400 mg/dL, or at least two standard deviations below normal, on at least two occasions
   NOTE: Immunoglobulin reference ranges vary depending on the age of the patient and the particular assay method utilized. The reference ranges from the respective laboratories should be used, where available. If the laboratory's reference ranges are not submitted with the immunoglobulin level results, the following standard reference ranges may be applied.

B. Documented inability to mount an adequate immunologic response to inciting antigens as evidenced by ONE (1) of the following examples (list not all inclusive): [ONE]
   ☑ Markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) can be used instead of a protein if the patient already has antibodies to tetanus and diphtheria. *An abnormal response is defined as less than a four-fold rise in antibody titer
   ☑ Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen such as pneumococcal vaccine (abnormal response is defined as less than a four-fold rise in antibody titer)
   NOTE: The diagnosis of immunodeficiency and post immunization titers must be taken in context with the clinical presentation of the patient, and may vary dependent on the type of vaccine given and the prior immunization history of the patient. The parameters listed above are examples of criteria for diagnosis of the primary immunodeficiency syndromes and therefore not an all-inclusive list.

C. Clinical history of significant recurrent infections meeting ONE (1) of the following criteria: Documentation required. [AT LEAST ONE]
   ☑ Two or more bacterial infections per year due to persistent and significant reduction in total IgG or IgG subclasses
   ☑ Unexplained recurrent or persistent severe bacterial infections despite antibiotic therapy
   ☑ Infections are responding inadequately to treatment with antibiotics and/or appropriate prophylaxis with antibiotics OR the member has multiple antibiotic hypersensitivities that interfere with treatment
   ☑ History of significant recurrent or persistent, severe bacterial infections (such as recurrent pneumonias, frequent episodes of bacterial infections such as sinusitis, otitis, bronchitis, skin structure infections, or infections of the gastrointestinal tract)
   ☑ For total IgG level is <200mg/dL or infants with BTK gene or absence of B lymphocytes: Documentation of an infection history not required.
Rationale for criteria A, B, and C: Per the American Academy of Allergy, Asthma and Immunology (AAAAI) Position Paper: Use of IVIG January 2005, the decision to treat with Ig should be based on: 1) abnormalities of serum immune globulin concentration, 2) clinical history of infections, and when appropriate and 3) the demonstrated inability to produce antibody normally following antigenic stimulation.

3. Age/Gender/Other restrictions [ALL APPLICABLE]
- Member meets age recommendation of SCIg product requested: [ONE]
  - Hizentra 20%; Gammagard Liquid 10%; Gammaplex 5% Liquid: 2 years and older
    - The safety and efficacy were not established in pediatric patients younger than 2 years.a-c
  - HyQvia; Gammaked; Gamunex-C 10%: 18 years and older
    - Efficacy and safety in pediatric patients using the subcutaneous route of administration have not been established.
- Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present

4. Step/Conservative Therapy/Other condition Requirements [ALL]
- Subcutaneous immunoglobulin required due to inability to continue receiving IVIg, such as but not limited to ONE (1) of the following: [ONE]
  - Trial, intolerance, or other clinical rationale explaining the inappropriateness to IVIg.
    - There is no medical evidence which demonstrates that SCIg is more effective than IVIg to improve and maintain immune globulin levels. Therefore, unless contraindicated, a trial of IVIG is required before SCIg products will be considered for authorization.
  - Poor venous access
    - SCIg products are often utilized in infants and children because of difficulty of intravenous (IV) access. Only a few have been specifically studied in pediatric populations. HyQvia is not licensed for use in children less than 18 years of age.
  - Infusion reactions not controlled by infusion rate adjustments or access site issues that are ongoing and unresolved by traditional means

5. Contraindications*/Exclusions/Discontinuations
Authorization will not be granted if ANY of the following conditions apply [ANY]
- Non-FDA approved indications
- Hypersensitivity to immune globulin or any component of the formulation
- IgA deficiency (with anti–IgA antibodies and history of hypersensitivity)
- Selective IgA deficiency; IgA-deficient individuals with antibodies against IgA
- Hyperprolinemia (type I or II); Hizentra® contain the stabilizer L-prolinea,c

6. Labs/Reports/Documentation required [ALL]
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the
member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

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

1. Initial Coverage Criteria

- Member currently meets ALL initial coverage criteria
- Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance

N/A

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

- Documentation of sustained clinical benefit of SCIg treatment as evidenced by medical records documenting current progress [AT LEAST ONE]
  - Objective monitoring of progress using metric assessment such as: Inflammatory Neuropathy Cause and Treatment (INCAT) scale, the Medical Research Council (MRC) scale, and activities of daily living (ADL) measurements
  - Medical Research Council (MRC) scale, Rankin score, Activities of Daily Living (ADL) scores
  - Objective findings on physical exam
  - Lab values showing normalized trough IgG (ideally greater than 600 mg/dL)

NOTE: Serum immunoglobulin G (IgG) levels can be drawn at any time relative to infusions once steady-state has been reached, which is usually after 6 to 12 weeks of SCIG therapy. The member's clinical condition should be the main determinant of the necessary IgG level, and different patients may require very different IgG levels to remain infection-free.

- Reduction/elimination of persistent bacterial infections
- Reduction/elimination of hospitalization related to infectious illness
- Stable disease or maintenance of desired clinical outcome

NOTE: Subjective improvement is insufficient to continue immune globulin treatment. If an objective clinical improvement does not occur, continued administration may not be considered medically necessary.

NOTE: Clinical monitoring may take precedence over laboratory monitoring. If clinical improvement is evident, then laboratory monitoring solely to guide immune globulin therapy is not necessary.  

According to a 2010 national guideline from Canada on immune globulin for primary immune deficiency, although higher trough levels of IVIg may be associated with clinical response; the goal of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.
of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.

- Requested dosing remains within FDA-labeled recommendations for respective indication
  - AND
  - Minimum effective dose being utilized for maintenance therapy (by decreasing the dose, increasing the frequency of administration, or implementing both strategies)

4. **Discontinuation of Treatment [ANY]**
   Discontinue treatment if ANY of the following conditions applies: [ANY]
   - Intolerable adverse effects or drug toxicity
   - Persistent and uncorrectable problems with adherence to treatment
   - Poor response to treatment as evidenced by physical findings and/or clinical symptoms
   - Contraindications/Exclusions to therapy
     - Non-FDA approved indications
     - Hypersensitivity to immune globulin or any component of the formulation
     - IgA deficiency (with anti–IgA antibodies and history of hypersensitivity)
     - Hyperprolinemia (type I or II); Hizentra® contain the stabilizer L-prolineă,e

1. **Recommended Dosage [ALL]**

- Dosage, frequency, site of administration, and duration of therapy is consistent with FDA-approved labeling in accordance to member’s specific condition. SCIg dosage must be individualized and is highly variable depending on the nature and severity of the disease and on the individual patient response. There is no absolute maximum dosage. Refer to FDA-approved labeling for dosage recommendations.

- **Adjustment(s) of dosage, frequency, site of administration, and duration of therapy** must be reasonable and appropriate based on condition and severity, alternative available treatments, and previous response to intravenous immune globulin therapy.

- **Conversion from IVIG**: To convert a patient from intravenous immune globulin (IVIg) to SCIg (by pump or rapid-push), the total monthly intravenous (IV) dose given is divided by four and given weekly. This approach will, after several months, result in steady-state immunoglobulin G (IgG) levels equivalent or higher than the levels achieved with an equivalent dose of IVIG. A dose of 100 mg/kg per week may be a good starting dose for most patients (adults and children).

- **For dosage or duration outside of the FDA-labeled indication**: Prescriber must submit supporting documentation in accordance to Molina Healthcare’s recognized pharmacology compendia and criteria for peer-reviewed clinical research for review. Refer to Off-Label Use of Drugs and Biologic Agents MCP-162.

2. **Authorization Limit [ALL]**

- **Quantity limit**: [BOTH]
  - One dose per month
  - Authorization dosing and quantity in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

- **Duration of initial authorization**: 6 months

- **Continuation of treatment**: Re-authorization for continuation of treatment is required every 12 months to determine continued need based on documented positive clinical response

3. **Route of Administration [ALL]**

- SCIg is administered subcutaneously and is considered a self-administered drug via a subcutaneous injection via a small, portable pump. Many patients can be readily trained to infuse subcutaneous immune globulin (SCIg) themselves at home, or parents may administer the infusions to their children. This is true in many older adults (>75 years) as well, including those on anticoagulant and/or platelet-inhibitor therapy. Adult patients can self-administer the infusion without the need to train another family member or schedule a home care visit.

- Per the manufacturer this drug may be administered at the patient’s convenience. Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.

- 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. Self-administered medications may not be dispensed
for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

**COVERAGE EXCLUSIONS**

All other uses of Subcutaneous Immune Globulin (SC Ig) that are not an FDA-approved indication or not included in the ‘Coverage Criteria’ section of this policy or supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage will not be authorized by this policy. *This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.*

- Applications of Subcutaneous Immune Globulin (SC Ig) for conditions other than primary immunodeficiencies are considered off-label in the United States and are not addressed in this policy. Refer to the off-label coverage for prescription drugs and biologics policy for complete criteria: **Off-Label Use of Drugs and Biologic Agents MCP-162**.

**SUMMARY**

**Primary Humoral Immune Deficiency**

Primary humoral immune deficiencies, a group of chronic disorders, are an FDA-approved indication for immune globulin therapy. Immune globulin is the standard treatment for primary immunodeficiency diseases (PI). Primary immunodeficiency diseases 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.

Other FDA-approved indications for immune globulin include idiopathic thrombocytopenic purpura (ITP), B-cell chronic lymphocytic leukemia (CLL), chronic inflammatory demyelinating polyneuropathy (CIDP), and Kawasaki syndrome as outlined above. In addition, in clinical practice, immune globulin is frequently used for treating a variety of off-label conditions in various therapeutic areas such as neurology, hematology, infectious disease, stem cell transplant, dermatology, and rheumatology. However, many of these off-label or proposed uses lack quality evidence of clinical benefit. Given the increasing demand and limited supply of immune globulin, along with the potential risks and relatively high cost of therapy, the indications for use of immune globulin require judicious consideration.

**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.

This policy addresses therapeutic use immune globulin G (IgG) an antibody produced by the B lymphocytes and administered subcutaneously. References to immune globulin within this guideline refer to immune globulin G (IgG). IgG products have been referred to in multiple ways, some of which are: immune globulin (IG), immunoglobulin, gamma globulin, and also by its route of administration - intravenous immune globulin (IV Ig), immune globulin intravenous (IGIV), subcutaneous immune globulin (SCIg), immune globulin subcutaneous (IgSC).

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 infusion (IV Ig)**
  Intravenous immune globulin (IV Ig) is an antibody-containing solution obtained from the pooled plasma of healthy blood donors, containing antibodies to greater than 10 million antigens. IV Ig has been used to correct immune
deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIg products have been approved by the FDA. These include the following:

- **BIVIGAM™** (Biotest Pharmaceuticals)
- **Carimune®** (ZLB Bioplasma)
- **Flebogamma®** (Grifols)
- **Gammagard®** (Baxter)
- **Gamunex-C** (Grifols)
- **Octagam®** (Octapharma)
- **Polygam® S/D** (Baxter)
- **Privigen®** (CSL Behring LLC)

At least one IVIg product is FDA-approved to treat the following conditions:

- B-cell chronic lymphocytic leukemia
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Immune (Idiopathic) thrombocytopenic purpura (ITP)
- Kawasaki syndrome
- Multifocal motor neuropathy (MMN)
- Primary humoral immunodeficiency

- **Subcutaneous infusion (SCIg)**
  Subcutaneous infusion of immune globulin (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**
  Intramuscular immune globulin (IMIg) 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.

**PITAL TRIALS**

- Safety and efficacy of IVIg for replacement therapy in patients with primary immunodeficiency diseases has been established in various clinical trials in adults and children who received IgIV once every 3 or 4 weeks for 12 months. The primary efficacy end point in these studies generally was the rate of serious acute bacterial infections (defined as pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess) per patient per year. Results indicated that the annual rate of serious acute bacterial infections in patients receiving IgIV was substantially less than 1 infection per patient year (0.0-0.1 infections per patient year). [per American Hospital Formulary Service (AHFS). Drug Information 2016. Immune Globulin]

**Reference:**

- Grifols Biologicals, Inc. *Flebogamma* 5% DIF (immune globulin intravenous [human]) prescribing information. Los Angeles, CA; 2009 Dec.
Safety and efficacy of Gammagard® Liquid 10% administered subcutaneously for replacement therapy in adults and children with primary immunodeficiency were evaluated in an open-label, prospective multicenter US study in 49 adult and pediatric patients, including those who had been receiving IGIV or another subcutaneous immune globulin preparation. All patients (regardless of their prior regimen) received an initial IV regimen of Gammagard® Liquid 10% (IV once every 3 or 4 weeks for 12 weeks) before being switched to subcutaneous Gammagard® Liquid 10%. The median duration of subcutaneous Gammagard® Liquid 10% therapy was 379 days (range 57-477 days). The annual rate of acute serious bacterial infections while patients were receiving subcutaneous Gammagard® Liquid 10% was 0.067 infections per patient per year and the annual rate of any infection (including viral and fungal infections) was 4.1 infections per patient per year.[per American Hospital Formulary Service (AHFS). Drug Information 2016. Immune Globulin]

Safety and efficacy of Hizentra® 20% immune globulin subcutaneous for replacement therapy in patients with primary immune deficiency were evaluated in an open-label, prospective, multicenter US study that included 49 adult and pediatric patients who were previously receiving a once-monthly regimen of IGIV and were switched to a once-weekly regimen of subcutaneous Hizentra® 20% given for 15 months. After a 3-month wash-in/wash-out period, the Hizentra® 20% dose was adjusted individually to achieve an IgG area under the concentration-time curve (AUC) that was equivalent to that attained with their previous IGIV therapy and the next 12 months of therapy was considered the efficacy period. In the modified intention-to-treat (MITT) population (38 patients who completed the 3-month wash-in/wash-out period and received at least 1 subcutaneous infusion of Hizentra® 20%), there were no serious bacterial infections (defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess) and the annual rate of any infection was 2.76 infections per patient per year. Safety and efficacy of Hizentra® 20% immune globulin subcutaneous also has been evaluated in an open-label, prospective, multicenter study in Europe that included 51 adult and pediatric patients with primary immunodeficiency who were previously receiving once-monthly IGIV (31 patients) or once-weekly immune globulin subcutaneous (20 patients) and were switched to once-weekly Hizentra® 20%. During the efficacy period, there were no serious bacterial infections and the annual rate of any infection was 5.18 infections per patient per year. [per American Hospital Formulary Service (AHFS). Drug Information 2016. Immune Globulin]

A 2008 review article concluded that SCIg therapy may be advantageous for selected populations of patients with primary antibody deficiency, including pregnant women, children, and patients with poor intravenous access. However, given that there are no RCTs for these patient types and conditions, there is insufficient evidence to support these uses of SCIg.

EVIDENCE-BASED PRACTICE GUIDELINES

The Immune Deficiency Foundation (IDF) Guidelines
In 2011, the Immune Deficiency Foundation (IDF) published guidelines on diagnosis and clinical care for primary immunodeficiency diseases. The guidelines support clinicians determine the possible type of PI and the screening diagnostic tests that should be ordered based on the site of infection. Although there are several different types of PI, the types that result in antibody production defects are those that are eligible for IgG therapy. The IDF recommends regular IgG therapy for patients with identified antibody deficiency disorders.

- The guidelines state the IVIG product should be dosed every 2-4 weeks and SCIG should be given every 1-14 days.
- It is recommended that an immunologist should participate in the determination of the proper dose and interval for IgG therapy in each patient.
- Should IgG treatment be required IV or SC administration are both recommended, and one product is not preferentially recommended over any other product.
Canadian Blood Services and Canada’s National Advisory Committee Guidelines

The Canadian Blood Services and Canada’s National Advisory Committee on Blood and Blood Products led a joint initiative to create guidelines for treatment of PI with immunoglobulin therapy. While the guidelines are primarily intended for health care professionals in Canada, many of their recommendations may be applied in other parts of the world, including the United States.

The National Advisory Committee on Blood and Blood Products and Canadian Blood Services issued practice guidelines on the use of IVIg in primary immune deficiency in 2010. The recommendations were based on interpretation of available evidence and where evidence was lacking, consensus of expert clinical opinion. The guidelines were constructed from an expert panel consisting of physicians from large pediatric and adult tertiary care centers who frequently cared for patients with primary immune deficiency, methodology experts, and members from the National Advisory Committee on Blood and Blood Products. The levels of evidence and grades used for each recommendation were adapted from the Canadian Task Force on Preventative Health Care. The levels of evidence describe the methodological rigor of the study, and the grades of recommendation comprise the level of evidence and clinical expertise. Relevant recommendations include the following:

- Give immunoglobulin to patients with primary antibody deficiency to reduce infections. (Level of evidence: I, Grade of recommendation: A)
- Give immunoglobulin to reduce hospitalization and organ damage. (I, A)
- Give immunoglobulin to improve survival and quality of life. (III, A)
- With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one manufacturer of IG over another for currently available products. (I to II-2, I)
- With respect to clinical efficacy for reducing infections, IVIg and SCIg preparations should be considered equivalent. (I and II, B)
- Do not give IMIG for replacement therapy for primary immune deficiency. (I, D)
- Start IVIG at a dose of 400 to 600 mg/kg per 4 weeks or SCIg at a dose of 100 to 150 mg/kg per week in most patients. (III, B)
- Patient and practitioners should be aware that patients with primary immune deficiency may require immunoglobulin replacement therapy indefinitely. (II-3, A)

Other recommendations in the 2010 guideline in regards to IVIg treatment of primary immune deficiencies include:

- If there is end-organ damage, the dose and/or frequency of immune globulin can be increased.
- Patients with primary immune deficiency may require immune globulin therapy indefinitely.
- Although higher trough levels of IVIg may be associated with clinical response; the goal of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.

A systematic review and one randomized controlled trial were used to evaluate the comparative efficacy and safety of IVIG and SCIG, and no statistically significant differences were found for severity and duration of infections. One report found that the patients treated with SCIg had a lower rate of infections (IVIG: 2.8 ± 2.0 infections/6 months; SCIg: 1.9 ± 1.9 infections/6 months), and two studies showed that SCIg was associated with improved quality of life. Studies were prospective and had small sample sizes. There were no statistically significant differences in trough levels.

**DEFINITIONS**

**Antibody:** Specialized gamma globulin proteins found in the blood or lymph that act as an immune defense against foreign agents (antigens).

**Antigen:** A substance, that when introduced into the body stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs.

**Immune globulin:** Replacement therapy for primary immunodeficiency; IgG antibodies against bacterial and viral agents; spectrum of antibodies that interact with and alter the activity immune system cells; antibodies capable of reacting with cells such as erythrocytes.
Intravenous infusion immune globulin (IVIg) is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIg products are available for clinical use in the United States.

### APPENDIX

**Appendix 1: Immune Globulin products available in the U.S. or Canada for SUBCUTANEOUS use**

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Route(s) of administration</th>
<th>Manufacturer (processed by)</th>
<th>Available in</th>
<th>Available vial sizes (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard Liquid</td>
<td>Subcutaneous† Intravenous</td>
<td>Baxalta</td>
<td>Canada United States</td>
<td>10, 25, 50, 100, 200, 300</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>Subcutaneous† Intravenous</td>
<td>Grifols</td>
<td>Canada United Kingdom</td>
<td>10, 25, 50, 100, 200, 400</td>
</tr>
<tr>
<td>Gammaked</td>
<td>Subcutaneous Intravenous</td>
<td>Kedrion</td>
<td>United States</td>
<td>10, 25, 50, 100, 200</td>
</tr>
<tr>
<td>Hizentra∆</td>
<td>Subcutaneous</td>
<td>CSL Behring</td>
<td>United Kingdom United States</td>
<td>5, 10, 20, 50</td>
</tr>
<tr>
<td>HyQvia◊</td>
<td>Subcutaneous</td>
<td>Baxalta</td>
<td>United Kingdom United States</td>
<td>25, 50, 100, 200, 300</td>
</tr>
</tbody>
</table>

¶ Subcutaneous route is licensed in the United States.

∆ Contains polysorbate 80 (concentration 8 to 30 mg/L), which is a potential allergen.

◊ Recombinant human hyaluronidase (rHH) is infused subcutaneously prior to immune globulin to increase dispersion and absorption of immune globulin. Description:

- 25 mL immune globulin 10% supplied with a separate 1.25 mL (200 units) vial of rHH
- 50 mL immune globulin 10% and separate 2.5 mL (400 units) rHH
- 100 mL immune globulin 10% and separate 5 mL (800 units) rHH
- 200 mL immune globulin 10% and separate 10 mL (1600 units) rHH
- 300 mL immune globulin 10% and separate 15 mL (2400 units) rHH

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE 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.

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<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg</td>
</tr>
</tbody>
</table>
### References

**Package Insert, FDA, Drug Compendia**


**Clinical Trials, Definitions, Peer-Reviewed Publications**


**Government Agencies, Professional Societies, and Other Authoritative Publications**


