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Coverage Policy

Cigna covers Immune Globulin Subcutaneous (IGSC) [Human] (Gammagard Liquid, Gammaked™, Gamunex-C®, Hizentra™, HyQvia) as medically necessary for Primary Immunodeficiency (PID) conditions listed below when ANY (1, 2, 3 or 4) of the following is present:

1) Hypogammaglobulinemia (including Common Variable Immunodeficiency [CVID]) when ALL of the following criteria are met (A, B, and C):

   A) Immunologic evaluation including documented serum IgG below the lower limits of normal of the laboratory’s reported value on at least two occasions

   B) Impaired Antibody Response (EITHER of the following):
      • lack of protective antibody titers (tetanus and diphtheria or HiB) measured 3–4 weeks after immunization
      • inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by EITHER of the following:
         ➢ age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
         ➢ age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
C) Recurrent Infection (ALL of the following):
   - history of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
   - evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
   - supporting diagnostic imaging and/or laboratory results where applicable

2) IgG subclass deficiency when ALL of the following criteria are met (A, B, and C):

   A) Immunologic evaluation including documented normal total serum IgG with one or more subclasses, excluding isolated subclass IgG4, below the lower limits of normal of the laboratory’s reported value on at least two occasions

   B) Impaired Antibody Response (EITHER of the following):
      - inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by EITHER of the following:
        - age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
        - age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)

   C) Recurrent Infection (ALL of the following)
      - history of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
      - evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
      - supporting diagnostic imaging and/or laboratory results where applicable

3) Specific antibody deficiency (SAD) when ALL of the following criteria are met (A, B, C, D, and E):

   A) Immunological evaluation including documented normal serum IgG, IgA, and IgM

   B) Normal responses to protein antigens (tetanus and diphtheria toxoid or HiB) measured 3–4 weeks after immunization

   C) Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by EITHER of the following:
      - age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
      - age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)

   D) Inadequate responsiveness to pneumococcal conjugate vaccine (Prevnar 13®) 4–8 weeks after vaccination as defined by EITHER of the following:
      - age < 6 years, < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
      - age ≥ 6 years, < 70% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)

   E) Recurrent Infection (ALL of the following):
      - history of severe recurrent and difficult to treat bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
      - evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
      - supporting diagnostic imaging and/or laboratory results where applicable

4) Selected Specific Primary Immunodeficiency Disorders when ONE of the following criteria is met:
   - agammaglobulinemia defined as serum IgG < 200 mg/dl
   - extremely low (< 2%) or absent B cell count (CD19*)
   - documentation of a recognized genetic defect supporting diagnosis*
   - transient hypogammaglobulinemia of infancy with serum immunoglobulins below the age-specific normal range and BOTH of the following:
• evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIG is only used for up to six months before re-evaluating the need for continued treatment)
• inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination defined as < 50% of serotypes are protective (i.e., ≥ 1.3 mcg/mL per serotype)
• hyperimmunoglobulemia E syndrome as evidenced by an elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and/or skin infections (abscess)

Cigna does NOT cover IGSC for any other indication because it is considered experimental, investigational or unproven.

In addition to the above criteria for PID, the following usage criteria also apply:

• The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to IVIG or IGSC therapy for the condition being addressed.
• Initial authorizations are restricted to three months unless otherwise specified within the individual criteria listed below by indication.

*See appendices for the following information:
• Appendix 1 – Standard Reference Ranges for Serum immunoglobulin Levels
• Appendix 2 – Standard Reference Ranges for Serum Immunoglobulin G Subclasses (G1, G2, G3, G4)
• Appendix 3 – Selected Genetic Based Primary Immunodeficiency (PID) Disorders

**FDA Approved Indication**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard Liquid</td>
<td>Gammard Liquid is an immune globulin infusion (human) indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.</td>
</tr>
<tr>
<td>Gammaked</td>
<td>Gammaked is an immune globulin injection (human) 10% liquid that is indicated as replacement therapy of primary humoral immunodeficiency. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>Gamunex-C is indicated as replacement therapy of primary humoral immunodeficiency (PID). This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.</td>
</tr>
<tr>
<td>Hizentra</td>
<td>Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the 8 humoral immune defect in congenital agammaglobulinemia, common variable 9 immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and 10 severe combined immunodeficiencies (FDA, 2011).</td>
</tr>
<tr>
<td>HyQvia</td>
<td>HyQvia is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies1,2. Limitation of Use: Safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia</td>
</tr>
</tbody>
</table>
### FDA Recommended Dosing

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard Liquid</td>
<td>Initial Dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Initial infusion rate is as follows: 40 kg body weight (BW) and greater - 30 mL/site at 20 mL/hr/site; under 40 kg BW - 20 mL/site at 15 mL/hr/site. Maintenance dose is based on clinical response and target IgG trough level. Maintenance infusion rate is as follows: 40 kg BW and greater - 30 mL/site at 20 to 30 mL/hr/site; under 40 kg BW - 20 mL/site at 15 to 20 mL/hr/site.</td>
</tr>
<tr>
<td>Gammaked</td>
<td>Subcutaneous dosing for PID only at 1.37 x current IV dose in mg/kg/IV dose interval in weeks at a rate of 20 mL/hr/site. Maintenance infusion rate has not been determined during the clinical study.</td>
</tr>
<tr>
<td>Gamunex C</td>
<td>The dose should be individualized based on the patient’s clinical response to Gamunex-C therapy and serum IgG trough levels. Begin treatment with Gamunex-C one week after the patient’s last IVIG infusion. Prior to switching treatment from IVIG to Gamunex-C, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments. Establish the initial weekly dose of Gamunex-C by converting the monthly IVIG dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to achieve a systemic serum IgG exposure (Area Under the Concentration-Time Curve [AUC]) not inferior to that of the previous IVIG treatment. If the patient has not been previously treated with IV Gamunex-C, convert the weekly IVIG dose by multiplying by 1.37, then dividing this dose into weekly doses based on the patient’s previous IVIG treatment interval. Monitor the patient’s clinical response, and adjust dose accordingly.</td>
</tr>
</tbody>
</table>
| Hizentra | The dose should be individualized based on the patient’s clinical response to Hizentra therapy and serum immunoglobulin G (IgG) trough levels.  
Start treatment with Hizentra one week after the patient’s last Immune Globulin Intravenous (Human) (IGIV) infusion. Before receiving treatment with Hizentra, patients need to have received IGIV treatment at regular intervals for at least 3 months. Before switching to Hizentra, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.  
Establish the initial weekly dose of Hizentra by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor. The goal is to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to that of the previous IGIV treatment  
To calculate the initial weekly dose of Hizentra, divide the previous IGIV dose by the number of weeks between doses during the patient’s IGIV treatment (e.g., 3 or 4); this is multiplied by the dose adjustment factor of 1.53.  
Initial Hizentra dose = Previous IGIV dose (in grams) x 1.53  
Number of weeks between IGIV doses  
To convert the Hizentra dose (in grams) to milliliters (mL), multiply the calculated dose (in grams) by 5.  
Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level. To determine if a dose adjustment should be considered, measure the patient’s serum IgG trough level 2 to 3 months after switching from IGIV to Hizentra. The target serum IgG trough level on weekly Hizentra treatment is projected to be approximately 290 mg/dL higher than the last trough level during prior IGIV therapy. |
**Brand Name** | **Recommended Dosing**
---|---
**HyQvia**

### Initiation of Treatment with HyQvia
- For patients previously on another IgG treatment, administer the first dose approximately one week after the last infusion of their previous treatment.
- Increase the dose and frequency from a 1-week dose to a 3- or 4-week dose (see ramp-up schedule in Table 1).
- Initiating treatment at a full monthly dose was not evaluated in the clinical trial.

For patients switching from Immune Globulin Intravenous (Human) [IGIV] treatment: Administer HyQvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up.

For patients naïve to IgG treatment or switching from Immune Globulin Subcutaneous (Human) [IGSC]: Administer HyQvia at 300 to 600 mg/kg at 3 to 4 week intervals, after initial ramp-up.

### Individualization of Dose

If HyQvia is administered at the same dose and frequency, the serum IgG levels from HyQvia should be comparable to serum IgG levels from intravenous treatment. For dose adjustment:
- Calculate the difference between the patient's serum IgG trough level during HyQvia treatment and the IgG trough level during the previous intravenous treatment.
- Find this difference (in mg/dL) in the columns of Table 2 and the corresponding amount (in mL) by which to increase or decrease the dose based on the patient's body weight and desired change in IgG trough level.

HyQvia can be used to administer a full therapeutic dose in one site up to every four weeks. Adjust the frequency and number of infusion sites taking into consideration volume, total infusion time, and tolerability. Adjust the frequency as needed so that the patient receives the same weekly equivalent dose.

In most clinical trials the main measure of efficacy of immune globulin was the annual rate of serious bacterial infections (e.g. pneumonia, sepsis, meningitis). Depending on the underlying condition, immune globulin therapy should be discontinued periodically (e.g., three months to one year) to reassess the status of the patient's humoral immune function. For example, in a patient with an IgG subclass deficiency or specific antibody deficiency with normal total IgG levels, pneumococcal polysaccharide vaccine (Pneumovax® 23) nonresponsiveness, and history of recurrent sinopulmonary infections not controlled with antibiotics, IVIG or IGSC may be discontinued one year after initial therapy and every two years thereafter. Three months after IVIG or IGSC are discontinued, immune response to vaccine (pneumococcal polysaccharide vaccine [Pneumovax® 23], protective antibody titers [tetanus and diphtheria or HiB], and/or pneumococcal conjugate vaccine [Prevnar 13®]) nonresponsiveness are reassessed. Reinitiation of IVIG or IGSC therapy will be based on the outcome of reassessment.
**Drug Availability**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard Liquid</td>
<td>Available vial sizes: 1GM, 2.5GM, 5GM, 10GM, 20GM, 30GM</td>
</tr>
<tr>
<td>Gammaked</td>
<td>Available vial sizes: 1GM, 2.5GM, 5GM, 10GM, 20GM</td>
</tr>
<tr>
<td>Gamunex-C</td>
<td>Available vial sizes: 1GM, 2.5GM, 5GM, 10GM, 20GM</td>
</tr>
<tr>
<td>Hizentra</td>
<td>Available vial sizes: 1GM, 2GM, 4GM, 10GM</td>
</tr>
<tr>
<td>Hyqvia</td>
<td>Available vial sizes: 2.5GM, 5GM, 10GM, 20GM, 30GM (Immune Globulin) with 200,400,600,800, 1200, 2400 respectively of units of Recombinant Human Hyaluronidase</td>
</tr>
</tbody>
</table>

**General Background**

**Disease Overview**
Primary immunodeficiency (PID) is a heterogeneous group of hereditary conditions, primarily characterized by an increased incidence, duration, and severity of infections. Many of these infections are caused by opportunistic organisms, and would not lead to overt illness in healthy individuals with intact immune systems. There are currently over 150 individual genetic mutations classified as PID. Some commonly recognized forms of PID include common variable immunodeficiency disease (CVID), agammaglobulinemia, Wiskott Aldrich syndrome, severe combined immunodeficiency, hyper IgM syndrome, hyper IgE syndrome, and IgA deficiency. Disease manifestation is largely dependent on the specific genetic mutation(s) involved. Some cases of PID are mild enough that they go undetected indefinitely, while other cases result in life-threatening infections. PID can also manifest itself in the form of arthritic conditions, diabetes mellitus, and various autoimmune diseases. Although the exact prevalence of PID is unknown, an estimated 25,000 to 50,000 people in the U.S. have the disease. Approximately 400 children are born with serious PID in the U.S each year. Although PID can act on any part of the immune system, approximately 50% of cases involve antibody deficiency.

**Guidelines**

**American Academy of Allergy Asthma and Immunology (AAAAI)**
The AAAAI Basic and Clinical Immunology Interest Section working group published a 2012 document on the use and interpretation of diagnostic vaccination in PID. The intent of the document was to provide guidance on the use of vaccination for diagnostic purposes in consideration of PIDD and to identify areas for future research (Orange, et al., 2012).

In a 2012 Choosing Wisely statement, AAAAI noted that low levels of immunoglobulins without impaired antigen-specific IgG antibody responses are not an indication for immunoglobulin replacement therapy. However, IgG levels < 150 mg/dL and genetically defined/suspected disorders may be an indication for therapy. Typically, measurement of IgG subclasses is not useful in defining the need for immunoglobulin therapy. AAAAI also stated that selective IgA deficiency is not an indication for IVIG therapy. In earlier publications AAAAI stated that selective IgA deficiency (SIGAD) is not an indication for IVIG replacement therapy. In some cases IVIG may be considered when there is poor specific IgG antibody production with or without IgG2 subclass deficiency or if there is inadequate response to antimicrobial therapy in a patient with a concomitant specific antibody defect. The use of gamma globulin therapy for the treatment of SIGAD without a demonstrable impairment of specific antibody formation is controversial (Orange, et al., 2006; Bonilla, et al., 2005). Regarding specific antibody deficiency (SAD), Bonilla et al. noted that mild antibody deficiencies are initially treated with antibiotic prophylaxis and generally do not require IVIG replacement for the control of recurrent bacterial infections. No evidence suggests that there are differences between the available products for subcutaneous use in regards to safety, efficacy or tolerability.

**Gammagard Liquid**

**Pharmacology:** Gammagard liquid supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Gammagard liquid also contains a spectrum
of antibodies capable of interacting with and altering the activity of cells of the immune system as well as antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in Gammagard liquid have not been fully elucidated.

**Gammaked**
**Pharmacology:** Gammaked supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viral, parasitic, mycoplasma agents, and their toxins. The mechanism of action in PI has not been fully elucidated. Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of Gammaked is IgG (98%) with a sub-class distribution of IgG1, IgG2, IgG3 and IgG4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

**Gamunex-C**
**Pharmacology:** Gamunex-C supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viral, parasitic, mycoplasma agents, and their toxins. The mechanism of action in PI has not been fully elucidated. The main component of Gamunex-C is IgG (≥98%) with a sub-class distribution of IgG1, IgG2, IgG3 and IgG4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

**Hizentra**
**Pharmacology:** Hizentra is a 200 mg/mL (20%) protein mixture containing at least 98% IgG. In PID, IgG administration replaces missing or inactivated antibodies, helping to normalize immune function. No studies have evaluated the bioavailability of Hizentra compared with IVIG or Vivaglobin. When given once weekly, Hizentra maintains fairly constant IgG concentrations, with lower peaks and higher troughs than IVIG given every 3 – 4 weeks.

**HyQvia**
**Pharmacology:** HyQvia ™ consists of a vial of 10% human immune globulin infusion and a vial of recombinant human hyaluronidase. The 10% human immune globulin (100 mg/mL) protein mixture contains at least 98% IgG. A vial of recombinant human hyaluronidase contains 160 units/mL of hyaluronidase, which is used to enhance the absorption of immune globulin into the subcutaneous tissue. The drug exposure and serum trough levels obtained with HyQvia ™, dosed at 108% of a patient’s previous intravenous immune globulin (IGIV) dose and administered every 3 to 4 weeks, are comparable with IGIV.

**Clinical Efficacy**
Abolhassani et al. (2012) conducted a systematic review and meta-analysis to compare the safety and efficacy of intravenous administration of immunoglobulin (IVIG) given in the hospital to home-administered subcutaneous immunoglobulin (SCIG) for the treatment of PID. The analysis included 47 articles (i.e., 10 randomized controlled trials, 17 prospective cohorts and 20 retrospective reviews) that met inclusion criteria (n=1484). Meta-analyses revealed the following: 1) significant preference of SCIG was achieved for serum IgG trough levels compared to IVIG therapy (p<0.01); 2) there was no significant difference in the serious infection rate of patients treated with IVIG vs. SCIG (p=0.04); and 3) there was a significant preference of SCIG over IVIG because of a decease in systemic adverse events (p<0.01). Quality of life and health perception were assessed by a variety of instruments including: Short Form 36 Health Survey (SF-36), Child Health Questionnaire-Parent Form 50 (CHQ-P50), Life Quality Index (LQI). Significant improvements (p=<0.0001 to p<0.05) were reported on the various outcomes (e.g., vitality, family activity, general health perceptions, health transition, mental health). The incidence of local reaction was higher in SCIG patients. The data on hospitalization rates (51 IVIG patients; 47 SCIG patients) were difficult to interpret because patients on SCIG received 28.3% less immunoglobulin than those on IVIG. The authors noted that very few studies were truly randomized or adequately controlled trials. In many cases, patient selection for SCIG was made by the patient due to adverse effects or dissatisfaction with IVIG which may have introduced a bias of over-enrolling patients who experienced an IVIG systemic effect.
Experimental, Investigational, Unproven Uses
Case series and randomized controlled trials have investigated IGSC for other conditions/indications, including the following:
- Chronic idiopathic demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Appendix 1
Standard Reference Ranges for Serum Immunoglobulin Levels

The following standard reference ranges may be used for evaluation if the testing laboratory’s reference ranges are not submitted.

<table>
<thead>
<tr>
<th>Normal Serum Immunoglobulin Levels (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>0 – 30 days</td>
</tr>
<tr>
<td>1 mo</td>
</tr>
<tr>
<td>2 mo</td>
</tr>
<tr>
<td>3 mo</td>
</tr>
<tr>
<td>4 mo</td>
</tr>
<tr>
<td>5 mo</td>
</tr>
<tr>
<td>6 mo</td>
</tr>
<tr>
<td>7 – 8 mo</td>
</tr>
<tr>
<td>1 yr</td>
</tr>
<tr>
<td>2 yr</td>
</tr>
<tr>
<td>3 yr</td>
</tr>
<tr>
<td>4 yr</td>
</tr>
<tr>
<td>5 – 7 yr</td>
</tr>
<tr>
<td>8 – 9 yr</td>
</tr>
<tr>
<td>10 yr &amp; older</td>
</tr>
</tbody>
</table>

Appendix 2

Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1, 2, 3, 4)

The following standard reference ranges may be used for evaluation if the testing laboratory’s reference ranges are not submitted.

<table>
<thead>
<tr>
<th>Age</th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord Blood</td>
<td>435-1084</td>
<td>143-453</td>
<td>27-146</td>
<td>1-47</td>
</tr>
<tr>
<td>0-2 months</td>
<td>218-498</td>
<td>40-167</td>
<td>4-23</td>
<td>1-33</td>
</tr>
<tr>
<td>3-5 months</td>
<td>143-394</td>
<td>23-147</td>
<td>4-70</td>
<td>1-14</td>
</tr>
<tr>
<td>6-8 months</td>
<td>190-388</td>
<td>37-60</td>
<td>12-62</td>
<td>1-16</td>
</tr>
<tr>
<td>9-23 months</td>
<td>288-880</td>
<td>30-327</td>
<td>13-82</td>
<td>1-65</td>
</tr>
<tr>
<td>2 years</td>
<td>170-950</td>
<td>22-440</td>
<td>4-69</td>
<td>0-120</td>
</tr>
<tr>
<td>3-4 years</td>
<td>290-1065</td>
<td>28-315</td>
<td>4-71</td>
<td>0-90</td>
</tr>
<tr>
<td>5-6 years</td>
<td>330-1065</td>
<td>57-345</td>
<td>8-126</td>
<td>2-116</td>
</tr>
<tr>
<td>7-8 years</td>
<td>225-1100</td>
<td>42-375</td>
<td>9-107</td>
<td>0-138</td>
</tr>
<tr>
<td>9-10 years</td>
<td>390-1235</td>
<td>61-430</td>
<td>10-98</td>
<td>1-95</td>
</tr>
<tr>
<td>11-12 years</td>
<td>380-1420</td>
<td>73-455</td>
<td>16-194</td>
<td>1-153</td>
</tr>
<tr>
<td>13-14 years</td>
<td>165-1440</td>
<td>71-460</td>
<td>12-178</td>
<td>2-143</td>
</tr>
<tr>
<td>15 years &amp; older</td>
<td>240-1118</td>
<td>124-549</td>
<td>21-134</td>
<td>7-89</td>
</tr>
</tbody>
</table>

Immunoglobulin G Subclass Levels (1, 2, 3, 4). Accessed April 2, 2013. Available at: http://www.aruplab.com/guides/ug/tests/0050577.jsp

Appendix 3

Selected Genetic Based Primary Immunodeficiency Syndrome (PID)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
</tr>
</thead>
</table>
| Autosomal recessive agammaglobulinemia (ARA)                   | • Recurrent sinopulmonary bacterial infections  
• Extremely low or absent IgG, IgM and IgA  
• IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired |
| Autosomal recessive hyperimmuno-globulin M syndrome (HIM)     | • Group of disease characterized by normal or elevated levels of serum IgM with low or absent IgG and IgA levels.  
• AICDA or UNG gene impaired |
| Combined immunodeficiency disorders (not all-inclusive)       | • Ataxia-telangiectasias (A-T)  
• Wiskott Aldrich syndrome (WAS)  
• DiGeorge syndrome (DGS)  
• Nijmegen breakage syndrome (NBS)  
• Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) |
| Congenital Hypogammaglobulinemia                              | • Late onset  
• Inducible Co-Stimulator (ICOS) impaired |
<table>
<thead>
<tr>
<th>Coverage Position Number: 8004</th>
</tr>
</thead>
</table>

| Congenital/X-linked agammaglobulinemia (XLA) | • Bruton’s Disease  
• BTK gene impaired |
|---------------------------------------------|--------------------------------------------------|
| Hyperimmuno-globulinemia E syndrome (HIES)  | • Includes recurrent lung and skin infections (e.g., chronic eczema)  
• Also known as job syndrome  
• Facies with coarse and/or asymmetric features  
• STAT3 mutation  |
| Hypogammaglobulinemia, unspecified         | • Primary hypogammaglobulinemia  
• Normal cellular immunity  
• Does not meet diagnostic criteria for a specific disorder  |
| ICF Syndrome                               | • Abnormal Facies  
• Respiratory Tract Infections  
• Hypogammaglobulinemia  
• Characteristic Chromosomal Abnormalities  |
| Specific Antibody Deficiency (SAD)         | • Generally does not require IVIG replacement for control of recurrent bacterial infections  
• Rare patients will have infection susceptibility with normal vaccine responses  |
| Selective IgG subclass deficiencies (IGGSD) | • Persistent absence of IgG1, IgG2, and/or IgG3  
• Generally does not require IVIG replacement for control of recurrent bacterial infections  
• Rare patients will have infection susceptibility with normal vaccine responses  |
| Severe combined immunodeficiency disorder (SCID) | • Complete absence of specific immunity  
• Most susceptible to entire range of possible pathogens  
• May be life threatening  |
| Transient hypogammaglobulinemia of infancy  | • Recurrent bacterial sinopulmonary infections and frequent viral illnesses  
• Only requires short-term IVIG replacement for recurrent severe bacterial infections  |

**Coding/Billing Information**

**Note:** 1) This list of codes may not be all-inclusive.  
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), non-lyophilized (e.g. liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J3590†</td>
<td>Unclassified biologics</td>
</tr>
</tbody>
</table>

†**Note:** Covered when medically necessary when used to represent HyQvia®
References


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