Immune Globulins Subcutaneous (SCIG) Prior Approval Criteria
January 2016

- Gammagard Liquid (immune globulin infusion 10% solution – Baxter Healthcare Corporation)
- Gammaked™ (immune globulin injection 10% caprylate/chromatography purified – Kedrion Biopharma, Inc. [manufactured by Talecris Biotherapeutics] [Grifols Therapeutics Inc])
- Gamunex®-C (immune globulin injection 10% caprylate/chromatography purified – Grifols Therapeutics, Inc)
- Hizentra® (immune globulin subcutaneous 20% liquid – CSL Behring)
- HyQvia (immune globulin infusion 10% with recombinant human hyaluronidase – Baxter Healthcare Corporation)
- Vivaglobin® (immune globulin subcutaneous 16% liquid – CSL Behring) discontinued

OVERVIEW
Immune globulin subcutaneous (SCIG) products are concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. SCIG supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The exact mechanism of SCIG in primary immune deficiency is not fully understood. SCIG products are indicated for replacement therapy in patients with primary humoral immune deficiency (PID), including, but is not limited to the humoral defect in the following conditions: common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) [congenital agammaglobulinemia], Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID). SCIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure. HyQvia limitation of use: safety and efficacy of chronic use of recombinant human hyaluronidase (rHu hyaluronidase) in HyQvia have not been established in conditions other than PID. Safety of HyQvia has not been established in children.

Hizentra is indicated as a subcutaneous (SC) infusion only, using an infusion pump. Gammagard Liquid, Gammaked, and Gamunex-C may be administered as a SC infusion or an intravenous (IV) infusion for PID. HyQvia is indicated for SC infusion only, with sequential infusion of the rHu hyaluronidase first and followed 10 minutes later with the immune globulin (IG) infusion using an infusion pump. The IG infusion provides the therapeutic effect of HyQvia. The rHu hyaluronidase acts locally to increase dispersion and absorption of the IG. When administered as an IV infusion, Gamunex-C and Gammaked are also indicated for idiopathic thrombocytopenia purpura (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP). Gammagard Liquid when given as an IV infusion is indicated for maintenance therapy in adults with multifocal motor neuropathy (MMN).

Gammagard Liquid, Gammaked, or Gamunex-C are self-administered once weekly or every 2 weeks by SC infusion. Hizentra is self-administered at regular intervals from daily up to every 2 weeks. The dose may be infused into multiple injection sites simultaneously. HyQvia is self-administered every 3 to 4 weeks after an initial dose ramp-up. The dose is infused into 1 or 2 injection sites. The volume per site with HyQvia is up to 600 mL in patients ≥ 40 kg and up to 300 mL in patients < 40 kg. The volume per

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injection site and flow rate is limited with any of the SCIG products and is adjusted individually. Generally, a more stable kinetic profile is noted with SCIG compared with the high peaks and low troughs noted with intravenous immune globulin (IVIG) therapy. Compared to IVIG, SCIG trough (pre-dose) levels are higher and peak serum levels are lower.

**Efficacy**

**Primary Humoral Immune Deficiency (PID)**

Gammagard Liquid, Hizentra, and Vivaglobin are indicated in children aged > 2 years and adults when given by SC infusion.\(^{1,4,5}\) Gammaked, Gamunex-C, and HyQvia are indicated in adults.\(^{2,3,6}\) HyQvia prescribing information notes that safety has not been established in children. Safety and efficacy of the SCIG products was established in patients with PID who were previously treated with monthly doses of IVIG.\(^{1-6,9-12}\) One week after the last dose of IVIG, patients were started on therapy with a SCIG product given weekly. Various methods were used for estimating the dose of SCIG and adjusting the dose to provide an adequate clinical response. Hizentra is indicated in patients who are switching from another SCIG product or from IVIG therapy.\(^{4}\) HyQvia is indicated in patients who are naïve to IG therapy or who are switching from another SCIG product or from IVIG therapy.\(^{6}\) An initial treatment interval and dosage ramp-up schedule is outlined in the prescribing information for initiating therapy with HyQvia. The first dose of HyQvia is given about one week after the last infusion of the patient’s previous IG treatment and is increased to an every 3- or 4-week dose. Initiating treatment with a full monthly dose was not evaluated in the pivotal clinical trial.

Therapy with SCIG products has been started in patients with PID who were not previously receiving IVIG or another SCIG product. A prospective, open-label, multicenter, single arm, 6-month study conducted outside the US assessed the treatment of 18 patients (1 to 70 years of age) with PID not previously treated with IG (SCIG or IVIG).\(^{13}\) Patients received Vivaglobin 100 mg/kg for 5 consecutive days and then patients self-infused Vivaglobin at a dose of 100 mg/kg as a single weekly infusion or divided into two infusions per week. The annualized rate of infection was lower during the study (3.95 infections per patient) than in the 6 months preceding the study (4.73 infections per patient). Other studies and guidelines indicate SCIG can be started in patients with PID who have not previously been treated with any IG replacement.\(^{14-17}\)

**Other Uses**

In contrast to IVIG, there are limited data available for off-label uses with SCIG. It is unclear if SC infusions will be effective for disorders that presumably benefit from immunomodulatory effects of peak serum IgG concentrations that result after IV infusion of high doses of IVIG for autoimmune or inflammatory diseases (see Guidelines).\(^{18}\) In case reports, case series, and small open-label studies SCIG has been effective in some patients with CIDP\(^{19-20}\) and MMN.\(^{21-23}\) In one small study, patients (n = 29) on maintenance therapy with IVIG (mean dose 0.3 g/kg/week) for CIDP were randomized to SCIG (Subcuvia® 16% product available in Europe) at a dose equivalent to their IVIG dose or to SC 0.9% sodium chloride injection given 2 or 3 times weekly for 12 weeks.\(^{24}\) The isokinetic muscle strength expressed as a percentage of the pretreatment level increased in the group receiving SCIG (5.5 ± 9.5%; P < 0.05) and declined in the saline group (14.4 ± 20.3%; P < 0.02). The difference between the two groups was significant (P < 0.004) in favor of the SCIG group. In an open-label follow up to the previous trial, 17 of 29 patients with CIDP who had responded, continued with SCIG (median dose 0.33 g/kg/week) for 12 months.\(^{25}\) After 12 months of SCIG, 4 patients had a decline in muscle strength, 10 had an increase, and 2 were unchanged. One Phase III trial is underway that compares Hizentra with placebo for maintenance therapy in patients with CIDP.\(^{26}\)

**Guidelines**
According to the 2005 Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency which was sponsored and developed by three national allergy and immunology societies (the American Academy of Allergy, Asthma, and Immunology [AAAAI], the American College of Allergy, Asthma and Immunology [ACAAI], and the Joint Council of Allergy, Asthma and Immunology [JCAAI]), IG may be given IV or SC. IVIG and SCIG are generally considered equivalent with regard to safety and efficacy. For standard replacement dosing, SCIG and IVIG replacement administration results in roughly equivalent trough IgG concentrations over time in PID. The occurrence of acute and delayed adverse effects with SCIG may be less than with IVIG, while the occurrence of acute or delayed local effects may be greater with SCIG than with IV administration. The choice between IV and SC administration may be influenced by: patient preference, problems with IV access, systemic adverse effects with IV administration, trough IgG levels, and physician or patient preference. The practice parameter notes that published data regarding safety, efficacy, and tolerability do not exist for all IG products when administered by the SC route. The practice parameter gives SC dosing recommendations for agammaglobulinemia or severe hypogammaglobulinemia. Evidence-based guidelines initiated by the Canadian Blood Services and The National Advisory Committee on Blood and Blood Products echo the AAAAI/ACAAI/JCAAI practice parameter. Another review from the Primary Immunodeficiency Committee of the AAAAI published in 2006 recommends SC infusions be limited to indications for PID since there is limited experience for other indications.

**POLICY STATEMENT**
Prior authorization is recommended for prescription benefit coverage of SCIG products (Gammagard liquid, Gammaked, Gamunex-C, Hizentra, HyQvia, and Vivaglobin). Because of the specialized skills required for evaluation and diagnosis of patients treated with SCIG as well as the monitoring required for adverse events and long-term efficacy, approval requires SCIG to be prescribed by or in consultation with a physician who specializes in the condition being treated. **All approvals are provided for 1 year in duration unless otherwise noted below.**

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**

A. Coverage of Gammagard Liquid, Gammaked, Gamunex-C, Hizentra, and Vivaglobin (all listed products except HyQvia) is recommended in those who meet the following criteria:

**Food and Drug Administration (FDA)-Approved Indications**

1. **Immunodeficiency, Primary Humoral (Treatment).** Approve in patients who meet the following criteria (a and b):
   a) SCIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND
   b) The patient has one of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):
      i. **CVID** AND the patient meets the following criteria (1, 2, 3, and 4):
          (1) Patient has a documented 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) according to the prescribing physician;
(2) Infections are responding inadequately to treatment with antibiotics\textsuperscript{14,32} and/or appropriate prophylaxis with antibiotics OR the patient has multiple antibiotic hypersensitivities that interfere with treatment\textsuperscript{18} according to the prescribing physician;

(3) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\textsuperscript{14} according to the prescribing physician;

(4) The patient has at least ONE of the following according to the prescribing physician:

- Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory);
- Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory; 
  Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\textsuperscript{31}
- 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.\textsuperscript{14,31,33-34}

ii. XLA (Bruton’s agammaglobulinemia, congenital agammaglobulinemia);\textsuperscript{14,35}

iii. SCID;\textsuperscript{14,36}

iv. Wiskott-Aldrich syndrome;\textsuperscript{18,37-37}

v. Hyper-Immunoglobulin M (IgM) syndromes, X-linked or autosomal recessive;\textsuperscript{18,39-41}

vi. Other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect\textsuperscript{14} (e.g., ataxia-telangiectasis,\textsuperscript{42} DiGeorge syndrome,\textsuperscript{39} nuclear factor κB essential modifier deficiency [NEMO]) AND the patient has frequent and severe infections according to the prescribing physician;

vii. Unspecified hypogammaglobulinemia AND the patient meets all of the following criteria (1, 2, 3, and 4):

1. Patient has a documented 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) according to the prescribing physician;\textsuperscript{14,18,31}

2. Infections are responding inadequately to treatment with antibiotics\textsuperscript{14,32} and/or appropriate prophylaxis with antibiotics OR the patient has multiple antibiotic hypersensitivities that interfere with treatment\textsuperscript{18} according to the prescribing physician;

3. Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\textsuperscript{14} according to the prescribing physician;

4. The patient has at least ONE of the following according to the prescribing physician:

- Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory);
- Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory; 
  Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\textsuperscript{31}
- 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.\textsuperscript{14,31,33-34}

B. Coverage of HyQvia is recommended in those who meet the following criteria:
FDA-Approved Indications

1. **Immunodeficiency, Primary Humoral (Treatment).** Approve in patients who meet the following criteria (a, b, and c):
   a) SCIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND
   b) The patient is ≥ 18 years of age; AND
   c) The patient has one of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):
      i. CVID\textsuperscript{14,28-30} AND the patient meets the following criteria (1, 2, 3, and 4):
         1. Patient has a documented 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) according to the prescribing physician;\textsuperscript{14,18,31}
         2. Infections are responding inadequately to treatment with antibiotics\textsuperscript{14,32} and/or appropriate prophylaxis with antibiotics OR the patient has multiple antibiotic hypersensitivities that interfere with treatment\textsuperscript{18} according to the prescribing physician;
         3. Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\textsuperscript{14} according to the prescribing physician;
         4. The patient has at least ONE of the following according to the prescribing physician:
            - Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory);
            - Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory;
            Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\textsuperscript{31}
            - 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.\textsuperscript{14,31,33-34}
      ii. XLA (Bruton’s agammaglobulinemia, congenital agammaglobulinemia);\textsuperscript{14,35}
      iii. SCID;\textsuperscript{14,36}
      iv. Wiskott-Aldrich syndrome;\textsuperscript{18,37-38}
      v. Hyper-Immunoglobulin M (IgM) syndromes, X-linked or autosomal recessive;\textsuperscript{18,39-41}
      vi. Other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect\textsuperscript{14} (e.g., ataxia-telangiectasis,\textsuperscript{42} DiGeorge syndrome,\textsuperscript{39} nuclear factor κB essential modifier deficiency [NEMO]) AND the patient has frequent and severe infections according to the prescribing physician;
      vii. Unspecified hypogammaglobulinemia AND the patient meets all of the following criteria (1, 2, 3, and 4):
         1. Patient has a documented 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) according to the prescribing physician;\textsuperscript{14,18,31}
         2. Infections are responding inadequately to treatment with antibiotics\textsuperscript{14,32} and/or appropriate prophylaxis with antibiotics or the patient has multiple antibiotic hypersensitivities that interfere with treatment\textsuperscript{18} according to the prescribing physician;
(3) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\textsuperscript{14} according to the prescribing physician; AND

(4) The patient has at least ONE of the following according to the prescribing physician:
- Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory);
- Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory;
  Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\textsuperscript{31}
- 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.\textsuperscript{14,31,33-34}

SCIG is indicated for the treatment of primary immunodeficiency associated with defects in humoral immunity which includes but is not limited to the following conditions: CVID, SCID, XLA, and Wiskott-Aldrich syndrome.\textsuperscript{1-6} Safety of HyQvia has not been established in pediatric patients.\textsuperscript{6} Gammagard Liquid and Hizentra are indicated for primary humoral immunodeficiency in patients ≥ 2 years of age.\textsuperscript{1,4} Safety and efficacy of SC administration of Gammaked and Gamunex-C for primary humoral immunodeficiency have not been established in pediatric patients, but safety and efficacy are established in pediatric patient when these products are given IV for primary humoral immunodeficiency and ITP.\textsuperscript{2,3} SCIG is used for replacement in primary immunodeficiency disorders where antibody production is significantly impaired to increase IgG levels and to prevent or control recurrent and chronic bacterial infections and to control symptoms.\textsuperscript{14,43}

Patients with PID are at high risk of developing acute and chronic bacterial infections. SCIG provides a broad spectrum of IgG antibodies that help prevent or attenuate infectious diseases. The use of SCIG in IgG subclass deficiencies (e.g., deficiencies of immunoglobulin A [IgA] or immunoglobulin E [IgE] in association with reduced IgG2 or IgG4) is controversial and is recommended only in those patients who also demonstrate a deficiency in the ability to form antibodies against a variety of polysaccharide and protein antigens.\textsuperscript{31-34}

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

SCIG has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality.** Evidence does not support use of SCIG.\textsuperscript{14,18,39,44} Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogamaglobulinemia have been excluded.\textsuperscript{14} Selective IgA deficiency may co-exist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency.\textsuperscript{14,18} Some of these patients with a concomitant specific antibody defect might benefit therapy with SCIG.

2. **HyQvia in Patients < 18 years of Age.** The safety of HyQvia in pediatric patients < 18 years of age has not been established.\textsuperscript{6} HyQvia is indicated in adults. In one prospective, open-label Phase III
clinical trial, eighty three patients aged 4 to 78 years with primary immunodeficiency received HyQvia. Six eleven of the patients were aged 2 to < 12 years, seventy were aged ≥ 12 years was 70).}

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

4. Hizentra® for subcutaneous infusion [prescribing information]. Kankakee, IL: CSL Behring LLC (manufactured by CSL Behring AG, Bern, Switzerland); January 2015.
5. Vivaglobin® injection [prescribing information]. Kankakee, IL: CSL Behring LLC (manufactured by CSL Behring GmbH, Marburg, Germany); April 2010.

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