



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Immune Globulin  
Subcutaneous [Human]  
(Gamunex-C<sup>®</sup>,  
Hizentra<sup>™</sup>, Vivaglobin<sup>®</sup>)**

**Effective Date..... 4/15/2011  
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Coverage Policy Number ..... 8004**

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## Hyperlink to Related Coverage Policies

Immune Globulin Intravenous (Human) (IVIG): Carimune<sup>™</sup> NF, Flebogamma<sup>®</sup>, Gammagard<sup>™</sup>, Gammar<sup>®</sup> P.I.V., Gamunex<sup>®</sup>, Gamunex-C<sup>®</sup>, Iveegam<sup>®</sup> EN, Octagam<sup>®</sup>, Panglobulin<sup>®</sup> NF, Polygam<sup>®</sup> S/D, Privigen<sup>®</sup>

## INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers Immune Globulin Subcutaneous [Human] (Gamunex-C<sup>®</sup>, Hizentra<sup>™</sup>, Vivaglobin<sup>®</sup>) as medically necessary for Primary Immunodeficiency (PID) conditions listed below when EITHER of the following is present:**

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

**A) Immunologic evaluation – (Any ONE of the following):**

- Serum IgG below the lower limits of normal on at least 2 occasions
- IgG sub-class deficiency of 1 or more serum IgG subclasses below the lower limits of normal on at least 2 occasions
- For Specific Antibody Deficiency (SAD), normal immunoglobulin levels

**B) Impaired Antibody Response (ONE of the following)**

- Lack of protective antibody titers (Tetanus and diphtheria or HiB) measured 3-4 weeks after immunization

- Inadequate response to polysaccharide vaccine (pneumococcal vaccine) in at least 30% of the serotypes tested as evidenced by either a post immunization antibody concentration of 1.3 mcg/mL or less OR less than a 4-fold increase over baseline

**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) 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<sup>+</sup>)
- documentation of a recognized genetic defect supporting diagnosis\* (\*For a list of selected genetic based Primary Immune Deficiency disorders, see Appendix 3)
- transient hypogammaglobulinemia of infancy with serum immunoglobulins below the age-specific normal range and evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIg is only used for up to 6 months before re-evaluating the need for continued treatment)
- Hyperimmunoglobulinemia E syndrome as evidenced by an elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and skin infections (abscess)
- Selective IgA deficiency documented by serum IgA less than 0.07 g/L with normal IgG, IgM in an individual older than 4 years with history of recurrent gastrointestinal infections

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 3 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 (1,2,3,4)

Appendix 3 – Selected Genetic Based Primary Immunodeficiency (PID) Disorders

## FDA Approved Indication

### Gamunex-C

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.

### Hizentra

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI).

### Vivaglobin

Vivaglobin Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

## **FDA Recommended Dosing**

### **Gamunex-C**

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.

### **Hizentra**

Begin treatment with Hizentra one week after the patient's last Immune Globulin Intravenous (Human) (IVIG) infusion. The initial weekly dose of Hizentra is calculated to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to that of the previous IVIG treatment. Initial dose = 1.53 x previous IVIG dose (in grams) divided by the number of weeks between IVIG doses. Measure the serum IgG trough level after 2 to 3 months of treatment with Hizentra. Adjust the dose to achieve serum IgG trough levels that are 1.3 times the trough level prior to the last IVIG treatment.

### **Vivaglobin**

All subjects who received Vivaglobin in the clinical trials had previously been treated with immune globulin. It is recommended that the patient start treatment with Vivaglobin one week after receiving a regularly scheduled IVIG infusion. The recommended weekly dose of Vivaglobin is 100 to 200 mg/kg body weight administered subcutaneously. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. As there can be differences in the half-life of IgG among patients with primary immune deficiencies, the dose and dosing interval of immunoglobulin therapy may vary.

## **Drug Availability**

### **Gamunex-C**

Gamunex-C is supplied in single-use, tamper evident vials (shrink band) containing the labeled amount of functionally active IgG. Gamunex-C is supplied in the following sizes: 10 mL, 25mL, 50mL, 100mL, and 200mL.

### **Hizentra**

Hizentra is supplied in a single-use, tamper-evident vial containing 0.2 grams of protein per mL of preservative-free liquid. The following dosage presentations are available: 5 mL; 10 mL; 20 mL.

### **Vivaglobin**

Vivaglobin is supplied in single-use vials containing 160 mg IgG per mL.

## **General Background**

### **Disease Overview**

Primary immunodeficiency 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 130 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. Primary Immunodeficiency Disease 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 (AAAI)**

Current recommendations (2009) of the AAAI for PID are in accordance with that of IVIG. However, it is recommended that individuals be taking IVIG before starting subcutaneous immune globulin treatment.

### **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 with a sub-class distribution of IgG1, IgG2, IgG3 and IgG4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

#### **Adverse Reactions**

The most common adverse reactions with subcutaneous use of Gamunex-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.

### **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.

#### **Adverse Reactions**

The most common adverse effects of Hizentra are local reactions, headache, vomiting, pain, and fatigue. Most local reactions were injection site reactions such as site swelling, redness, warmth, pain, or itching. Local reactions are usually mild to moderate in severity. The risk of local reactions appears similar with Hizentra and Vivaglobin, based on a small crossover study. Serious adverse effects reported with IVIG may also occur with Hizentra, including hypersensitivity reactions, potentially fatal renal toxicity, thrombotic events, aseptic meningitis syndrome, hemolysis, and transfusion-related acute lung injury. Therapy with Hizentra may reduce the efficacy of live attenuated vaccines. However, live attenuated vaccines are contraindicated in patients with PID, because of the increased risk of serious infection or death in these patients.

### **Vivaglobin**

#### **Pharmacology**

Vivaglobin is a 16% protein mixture containing at least 96% IgG. Administration of IgG replaces missing or inactivated antibodies, helping to normalize immune function in antibody deficient PID. The bioavailability of Vivaglobin is approximately 73% when compared to intravenous administration of immune globulin. When administered weekly, Vivaglobin results in lower peak and higher trough IgG levels than IVIG administered every 3-4 weeks.

#### **Adverse Reactions**

Most adverse events that occur with Vivaglobin are common to IVIG. The most common adverse events associated with Vivaglobin are infusion site reactions, consisting of swelling, itching, and redness. All reported infusion site reactions were mild to moderate in severity. The incidence and severity of infusion site reactions decreased with ongoing dosing. The only reported drug interaction for Vivaglobin is decreased efficacy of live, attenuated vaccines - prescribers should be made aware of this interaction prior to administering vaccines. Vivaglobin should not be used in individuals with selective IgA deficiencies who have antibodies against IgA.

*The FDA is encouraging the transition from Vivaglobin to Hizentra because Vivaglobin manufacturing for the United States will end by the close of 2011.*

**Note: The standard threshold for lower limit of normal is two standard deviations below the mean. This number may vary among different laboratories.**

**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.

<b>Normal Serum Immunoglobulin Levels (mg/dL)</b>			
<b>Age</b>	<b>IgA</b>	<b>IgG</b>	<b>IgM</b>
0 – 30 days	1 – 7	<b>611 – 1542</b>	0 – 24
1 mo	1 – 53	<b>241 – 870</b>	19 – 83
2 mo	3 – 47	<b>198 – 577</b>	16 – 100
3 mo	5 – 46	<b>169 – 558</b>	23 – 85
4 mo	4 – 72	<b>188 – 536</b>	26 – 96
5 mo	8 – 83	<b>165 – 781</b>	31 – 103
6 mo	8 – 67	<b>206 – 676</b>	33 – 97
7 – 8 mo	11 – 89	<b>208 – 868</b>	32 – 120
9 – 11 mo	16 – 83	<b>282 – 1026</b>	39 – 142
1 yr	14 – 105	<b>331 – 1164</b>	41 – 164
2 yr	14 – 122	<b>407 – 1009</b>	46 – 160
3 yr	22 – 157	<b>423 – 1090</b>	45 – 190
4 yr	25 – 152	<b>444 – 1187</b>	41 – 186
5 – 7 yr	33 – 200	<b>608 – 1229</b>	46 – 197
8 – 9 yr	45 – 234	<b>584 – 1509</b>	49 – 230
10 yr & older	68 – 378	<b>768 – 1632</b>	60 – 263

Immunoglobulins, Serum Quantitative. Accessed April 6, 2009.  
 Available at: <http://www.aruplab.com/guides/ug/tests/0050630.jsp>

**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.

<b>Normal Serum Immunoglobulin G Subclass Levels (mg/dL)</b>				
<b>Age</b>	<b>IgG 1</b>	<b>IgG 2</b>	<b>IgG 3</b>	<b>IgG 4</b>
Cord Blood	435-1084	143-453	27-146	1-47
0-2 months	218-498	40-167	4-23	1-33

3-5 months	143-394	23-147	4-70	1-14
6-8 months	190-388	37-60	12-62	1-16
9-23 months	288-880	30-327	13-82	1-65
2 years	170-950	22-440	4-69	0-120
3-4 years	290-1065	28-315	4-71	0-90
5-6 years	330-1065	57-345	8-126	2-116
7-8 years	225-1100	42-375	9-107	0-138
9-10 years	390-1235	61-430	10-98	1-95
11-12 years	380-1420	73-455	16-194	1-153
13-14 years	165-1440	71-460	12-178	2-143
15 years & older	240-1118	124-549	21-134	7-89

Immunoglobulin G Subclass Levels (1,2,3,4). Accessed April 6, 2009.  
Available at: <http://www.aruplab.com/guides/ug/tests/0050577.jsp>

### **Appendix 3**

#### **Selected Genetic Based Primary Immunodeficiency Syndrome (PID)**

<b>Condition</b>	<b>Features</b>
<b>Congenital / X-linked agammaglobulinemia-XLA</b>	Bruton's Disease- BTK gene impaired
<b>Autosomal recessive agammaglobulinemia - ARA</b>	IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired
<b>Autosomal recessive hyperimmuno-globulin M syndrome (HIM)</b>	AICDA or UNG gene impaired
<b>Congenital Hypogammaglobulinemia</b>	late onset, ICOS impaired
<b>ICF Syndrome</b>	<ul style="list-style-type: none"> <li>• Abnormal Facies</li> <li>• Respiratory Tract Infections</li> <li>• Hypogammaglobulinemia</li> <li>• Characteristic Chromosomal Abnormalities</li> </ul>
<b>Specific Antibody Deficiency (SAD)</b>	<ul style="list-style-type: none"> <li>• generally does not require IVIG replacement for control of recurrent bacterial infections</li> <li>• Rare patients will have infection susceptibility with normal vaccine responses</li> </ul>
<b>Hypogammaglobulinemia, unspecified</b>	N/A
<b>Transient hypogammaglobulinemia of infancy</b>	only requires short-term IVIG replacement for recurrent severe bacterial infections
<b>Selective IgG subclass deficiencies (IGGSD)</b>	<ul style="list-style-type: none"> <li>• persistent absence of IgG1, IgG2, and/or IgG3</li> <li>• generally does not require IVIG replacement for control of recurrent bacterial infections</li> <li>• Rare patients will have infection</li> </ul>

	susceptibility with normal vaccine responses
<b>Combined immunodeficiency disorders</b> (not all-inclusive)	<ul style="list-style-type: none"> <li>• ataxia-telangiectasia (<b>A-T</b>)</li> <li>• Wiskott Aldrich syndrome (<b>WAS</b>),</li> <li>• DiGeorge syndrome (<b>DGS</b>)</li> <li>• Nijmegen breakage syndrome (<b>NBS</b>)</li> <li>• (<b>WHIM</b>) warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis</li> </ul>
<b>Severe combined immunodeficiency disorder (SCID)</b>	N/A
<b>Hyperimmuno-globulinemia E syndrome (HIES)</b>	N/A

## Coding/Billing Information

**Note:** This list of codes may not be all inconclusive

**Covered when medically necessary:**

HCPCS Codes	Description
J1562	Injection, immune globulin (Vivaglobin), 100 mg
J1559	Injection, immune globulin (hizentra), 100 mg
J1561 <sup>†</sup>	Injection, immune globulin (Gamunex), intravenous, nonlyophilized (e.g.liquid), 500 mg

<sup>†</sup>**Note:** This code is used to report Gamunex (administered intravenously) and Gamunex-C (administered subcutaneously).

ICD-9-CM Diagnosis Codes	Description
279.00	Hypogammaglobulinemia, unspecified
279.03	Other selective immunoglobulin deficiencies
279.04	Congenital hypogammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.09	Other, deficiency of humoral immunity
279.11	DiGeorge's syndrome
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
279.4	Autoimmune disease, not elsewhere classified
334.8	Other spinocerebellar diseases

## References

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	4/15/2008	8004	Immune Globulin Subcutaneous [Human] (Vivaglobin®)
Great-West Healthcare	12/2007	P02.104.2	Immune Globulins

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