



# 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 Stem-Cell Transplantation for Primary Immunodeficiency Disorders**

**Effective Date ..... 7/15/2011**  
**Next Review Date.....7/15/2012**  
**Coverage Policy Number ..... 0378**

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Immune Globulin Intravenous (Human) (IGIV): Carimune™ NF, Flebogamma®, Gammagard™, Gammar® P.I.V., Gamunex®, Iivegam® EN, Octagam®, Panglobulin® NF, Polygam® S/D, Privigen®  
Transplant Donor Charges  
Umbilical Cord Blood Banking

## INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA covers allogeneic hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of primary immunodeficiency disorders.**

## General Background

Immunodeficiency disorders, also known as primary, congenital, or inherited immunodeficiency disorders, are conditions where there is a failure of the immune system to fight invading microorganisms or tumors. The term primary denotes the genetic nature of the defects, differentiating them from secondary, or acquired, immunodeficiencies caused by malnutrition, infection, chemotherapy, or other external agents (Lindegren, 2004). The disorders vary in the severity and spectrum of symptoms, but without effective and early treatment they can be fatal (Lindegren, 2004).

Primary immunodeficiency disorders are often classified according to the affected components of the immune system or immunologic phenotype (Lindegren, 2004; Notarangelo, 2006). Although over 120 primary immunodeficiency syndromes have been identified, less than 20 disorders account for over 90% of the known cases (Lindegren, 2004). Some of the more commonly occurring disorders include the following:

- **B-cell (antibody) deficiencies**
  - X-linked agammaglobulinemia
  - combined variable immunodeficiency (CVID)
  - hyper-IgM syndrome
  - selective IgA deficiency
- **Combined T-cell and B-cell (antibody) deficiencies**
  - severe combined immunodeficiency (SCID)
  - partial combined immunodeficiency (CID)
  - Wiskott-Aldrich syndrome (WAS)
- **T-Cell deficiencies**
  - DiGeorge syndrome
- **Defective phagocytes**
  - Chediak-Higashi syndrome
  - chronic granulomatous disease
  - leukocyte adhesion defect
- **Complement deficiencies**
  - hereditary angioedema
- **Deficiencies/cause unknown**
  - hyper-IgE syndrome
  - chronic mucocutaneous candidiasis
- **Defects in innate immunity**
  - anhidrotic ectodermal hyperplasia (NEMO deficiency)
  - X-linked IgM syndrome
- **Autoinflammatory disorders**
  - tumor necrosis factor (TNF) receptor periodic fever
  - hyper-IgD syndrome

Treatment varies depending on the specific disorder. Allogeneic hematopoietic stem-cell transplantation (HSCT) has been proposed as a potentially curative treatment option for primary immunodeficiency disorders.

### **Stem-Cell Transplantation**

Stem-cell transplantation refers to transplantation of hematopoietic stem-cells (HSC) into an individual. HSC transplantation (HSCT) can be either autologous (using the individual's own stem cells) or allogeneic (using stem cells from a donor).

Data from randomized controlled trials are lacking; however, there are a number of observational and descriptive studies in the published peer-reviewed scientific literature demonstrating improved survival with the use of allogeneic HSCT for the treatment of inherited immunodeficiency disorders (Petrovic, 2009; Diaz de Heredia, 2008; Cohen, 2007; Sato, 2007). Overall survival (OS) varied from 100%–73% at four-, and five-years, respectively.

**SCID:** Allogeneic HSCT is the treatment of choice for SCID variants, as well as for several other inherited immunodeficiencies (Diaz de Heredia, 2008; National Institutes of Health [NIH], 2008; Velardi, 2007). With a human leukocyte antigen (HLA)-identical sibling, the probability of survival approaches 100%, with less favorable results for patients transplanted from an unrelated volunteer or an HLA–partially matched relative. Several retrospective reviews reflect long-term survival of 90%–92.3% (i.e., up to 11 years) for individuals with allogeneic HSCT using an HLA-matched donor (Friedrich, 2009; Grunebaum, 2006). Use of reduced-intensity conditioning with HLA-identical donor allogeneic HSCT to improve long-term immune reconstitution is an evolving therapy for this condition (Cancrini, 2010).

**Wiskott-Adrich Syndrome (WAS):** The rarity of WAS and variety of donor sources used (e.g., matched sibling, matched and mismatched unrelated adult hematopoietic stem cell transplantation (HSCT), haploidentical related, and matched and mismatched cord blood) necessitate cooperative registry studies to analyze even straightforward outcomes such as survival. Complete donor chimerism cures the life threatening manifestations of WAS, including hemorrhage, infection, autoimmunity and malignancy, and can be achieved using myeloablative doses of chemotherapy (Pai, 2010). Several retrospective reviews and an analysis of registry data reflect long-term event-free (EFS) and overall survival (OS) with the use of allogeneic hematopoietic stem-cell transplantation (HSCT) (Ozsahin, 2008; Munoz, 2007; Kobayashi, 2006). In a retrospective multi-center study of 96 patients undergoing allogeneic HSCT, Ozsahin et al. reported an overall seven-year event-free survival (EFS) of 75%, with EFS rates of 88% and 71%, respectively, for patients with matched sibling, and unrelated donors.

**Chediak-Higashi Syndrome:** Allogeneic HSCT is considered a definitive treatment for this disorder (Nichols, 2002). Eapen et al. (2007) performed a retrospective analysis of 35 patients who underwent an allogeneic HSCT. With a median follow-up of 6.5 years, the five-year probability of OS was 62%.

**Chronic Granulomatous Disease (CGD):** Currently the only curative therapy for CGD is allogeneic HSCT, although this has been infrequently offered due to the risk of procedure-related morbidity and mortality (Kang, 2011). Soncini et al. (2009) reported the long-term survival outcomes of 20 patients with CGD who underwent allogeneic HSCT between 1998 and 2007. All patients engrafted; 90% were alive with normal neutrophil function at a median of 61 months.

**Leukocyte Adhesion Deficiency:** Qasim et al. (2009) retrospectively analyzed the outcomes of 36 children with leukocyte adhesion deficiency that underwent allogeneic HSCT. At a median follow-up of 62 months, overall survival (OS) was 75%.

#### Literature Review

**Summary:** Although data are not robust, allogeneic HSCT is the only potentially curative treatment for inherited immunodeficiency disorders. Improved long-term overall- and event-free survival have been noted with uncontrolled cohort and retrospective studies. Allogeneic HSCT is considered an acceptable treatment option for selected individuals.

#### Contraindications

Many factors affect the outcome of a tissue transplant. The selection process is designed to obtain the best result for each individual. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two<sup>†</sup>

#### Professional Societies/Organizations

**National Institute of Child Health and Human Development (NICHD):** The NICHD (2008) notes that for several life-threatening immunodeficiencies, bone marrow transplantation offers the chance of a dramatic, complete, and permanent cure.

**National Marrow Donor Program (NMDP):** The NMDP notes that severe combined immunodeficiency (all types) and other inherited immune system disorders, including Wiskott-Aldrich syndrome are treatable by allogeneic hematopoietic cell transplantation.

#### Summary

Although the data are not robust, allogeneic hematopoietic stem-cell transplantation (HSCT) is considered an acceptable treatment option for selected individuals with primary immunodeficiency disorders.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary when used to report allogeneic bone marrow or blood-derived stem cell procedures:**

<b>CPT<sup>®</sup>* Codes</b>	<b>Description</b>
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

<b>HCPCS Codes</b>	<b>Description</b>
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days or pre-and post-transplant care in the global definition

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
277.6	Other deficiencies of circulating enzymes
279.00	Hypogammaglobulinemia, unspecified
279.01	Selective IgA immunodeficiency
279.02	Selective IgM immunodeficiency
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
279.3	Unspecified immunity deficiency
288.1	Functional disorders of polymorphonuclear neutrophils
288.2	Genetic anomalies of leukocytes
757.31	Congenital ectodermal dysplasia
	Multiple/Varied

**\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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## Policy History

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<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	7/15/2008	0378	Stem-Cell Transplant for Primary Immunodeficiency Disorders

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