



# 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 Sickle Cell Disease and Thalassemia Major**

**Effective Date ..... 7/15/2011**  
**Next Review Date ..... 7/15/2012**  
**Coverage Policy Number ..... 0464**

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## Hyperlink to Related Coverage Policies

Donor Leukocyte Infusion  
 Genetic Testing for Hemoglobinopathies  
 Transplant Donor Charges  
 Umbilical Cord Blood Banking

### 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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)- matched donor (i.e., at least five of six match of the HLA-A, HLA-B, and HLA-DRB1 antigens ) as medically necessary for the treatment of a child or young adult at increased risk of complications of sickle cell disease (SCD) or thalassemia major.**

**CIGNA does not cover non-myeloablative allogeneic HSCT for a child or young adult with SCD or thalassemia major because it is considered experimental, investigational or unproven.**

**CIGNA does not cover HSCT for an adult with SCD or thalassemia major because it is considered experimental, investigational or unproven.**

## General Background

Hemoglobinopathies are a group of rare, inherited disorders involving abnormal structure of the hemoglobin molecule. Several hundred unusual hemoglobins have been identified. Clinically significant variants include hemoglobin S-C disease, sickle cell anemia, various types of thalassemia, hemoglobin C, and hemoglobin E. (National Institutes of Health [NIH], 2011a; Chiu, 2005; Sickle Cell Disease Association of America [SCDAA], 2011).

Sickle cell disease (SCD) encompasses many sickling syndromes caused by abnormal sickle hemoglobin. The most common are sickle cell anemia (Hb SS), sickle-hemoglobin C disease (Hb SC), sickle-beta plus thalassemia, and sickle-beta zero thalassemia (NIH, 2010a,b; Quinn, 2005). The disease follows a variable clinical course which may include complications such as severe anemia, painful sickle cell crises, organ damage due to iron overload, acute chest syndrome, refractory pain, stroke, and premature death. Accepted treatment options include chronic blood transfusions, hydroxyurea, and allogeneic HSCT for selected children and young adults.

### **Stem-Cell Transplantation**

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor 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).

In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

**Myeloablative Allogeneic HSCT:** Myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potentially curative treatment option for selected individuals with sickle cell disease or thalassemia major (Novelli, 2011; Bhatia, 2008; Krishnamurti, 2008; Iannone, 2005; Walters, 2004; Quinn, 2004). HSCT involves replacing the deformed red blood cells and the cells that produce them with normal cells from a healthy donor. Research to date has demonstrated that successful engraftment of normal donor hematopoietic stem cells prevents additional pathological effects of SCD. Full donor chimerism is not necessary to achieve this effect (Iannone, 2005; Krishnamurti, 2008).

The optimal timing for marrow transplantation in the course of SCD remains uncertain, in part, because of the unpredictable nature and clinical heterogeneity of the disease (Hoppe, 2004; Walters, 2004). Selection criteria for optimal candidates continue to evolve; however, children and young adults, generally before the age of 21 years are considered the most appropriate candidates. Indications for HSCT have been empirically determined from prognostic factors derived from studies of the natural history of SCD. The most common indications for which patients with SCD have undergone HSCT are a history of stroke, recurrent acute chest syndrome, or frequent vaso-occlusive episodes (Novelli, 2011). Children and young adults who have severe complications (e.g. stroke, recurrent acute coronary syndrome [ACS], refractory pain) and have a human-leukocyte antigen (HLA)-matched donor are the best candidates for transplantation (Panepinto, 2007). Very few adults are considered for transplantation due to existing comorbidities and toxicity of treatment (Walters, 2005).

Data from randomized controlled trials are lacking; however, several case series, retrospective reviews, and registry analyses have demonstrated improved overall- and event-free survival with allogeneic HSCT, primarily in children  $\leq 18$  years (Bernauldin, 2007; Panepinto, 2007; Locatelli, 2004; Walters, 2000). Five and six-year probabilities of disease-free-, and overall survival were 85%–86%, and 93%–97%, respectively (Novelli, 2011; Bernauldin, 2007; Panepinto, 2007; Walters, 2000). Current research is focused on improving the applicability of HSCT to a greater proportion of patients with SCD by the development of novel conditioning regimens minimizing myeloablation and the use of novel sources of hematopoietic stem cells such as umbilical cord blood (Novelli, 2011).

### **Summary**

**Myeloablative Allogeneic HSCT for SCD:** Although data are not robust, myeloablative allogeneic HSCT is considered an appropriate treatment option for selected children and young adults at high risk of complications of SCD. There are scarce data in the published, peer-reviewed scientific literature regarding safety and effectiveness of myeloablative allogeneic HSCT for use in the adult population. At this time the role of myeloablative allogeneic HSCT for has not been established for this indication.

**Non-Myeloablative Allogeneic HSCT:** Toxicity of myeloablative conditioning regimens and the finding that mixed chimerism can cure SCD have prompted recent studies using reduced toxicity conditioning regimens that do not ablate host hematopoiesis. At present, study populations include very small numbers of adults and children who have evidence of organ damage from vaso-occlusion or iron overload as a result of chronic transfusion therapy. Mortality related to graft-versus-host disease (GVHD) and graft rejection continues to be a

complication related to this therapy. Published reports have confirmed improved safety, but the majority of these transplants are unsuccessful because of graft failure (Horwitz, 2007). Although investigations are continuing, it has been difficult to identify a regimen that is sufficiently immunosuppressive to ensure stable engraftment of donor cells, yet also meets the objective of reduced toxicity with a risk that is distinguishable from conventional allografting (Walters, 2005).

Krishnamurti (2008) evaluated outcomes for seven patients with severe sickle cell disease (SCD) who underwent allogeneic hematopoietic stem-cell transplantation (HSCT) with reduced-intensity conditioning. Median patient age was eight years. At one year post transplantation six of seven patients had mixed donor chimerism. At a follow-up of 2-8.5 years after transplantation, all patients are alive, are off immunosuppression, and six of seven patients have no laboratory or clinical evidence of disease.

Horwitz et al. (2007) reported the outcomes of two adult patients with SCD who underwent total-body irradiation followed by fludarabine-based nonmyeloablative conditioning and allogeneic HSCT. Both patients achieved complete donor chimerism, have normal blood counts and are on no immunosuppressive drugs.

Horan et al. (2005) reported the results of four consecutive patients who received allogeneic HSCT with non-myeloablative conditioning. Three patients had SCD (two patients had Hb SS; one patient had Hb C), and one patient had thalassemia major. Donors were human leukocyte antigen (HLA)-identical siblings in all cases. At three months post-transplantation, all patients had evidence of donor myeloid chimerism (range 15–100%); however, after post-transplantation, immunosuppression was discontinued and graft rejection occurred in three recipients. At 27 months' follow-up, one patient was doing well, with full donor chimerism. One patient received a second HSCT for graft failure and died at 52 days post-HSCT due to pneumonia and intractable heart failure. The other patients remained alive but without significant donor chimerism.

Iannone et al. (2003) analyzed the outcomes of six patients with SCD and one patient with thalassemia major who received non-myeloablative conditioning with allogeneic HSCT. Prior complications before transplantation in patients with SCD included cerebral infarct (n=3), frequent painful crises (n=2) and acute chest syndrome (n=1). All donors were HLA-identical siblings; of these, four had sickle cell trait. Two months after transplantation, six of seven patients had evidence of donor chimerism; one patient did not engraft. After post-transplantation, immunosuppression was tapered; however, there was a nonfatal loss of donor graft. All patients experienced autologous hematopoietic recovery, and there was disease recurrence.

## Summary

**Non-Myeloablative Allogeneic HSCT for SCD:** The ability to draw conclusions regarding the effectiveness of this therapy is limited by small study size, use of heterogeneous conditioning regimens, and study design. Although a subject of ongoing study, the role of this therapy has not yet been established for this indication.

## Thalassemia

Thalassemia is a hereditary anemia resulting from defects in hemoglobin production. These defects result in low levels of hemoglobin being produced and excessive destruction of red blood cells. There are two types of thalassemia, alpha and beta, depending on which of the two hemoglobin chains is involved. Alpha and beta thalassemia have both mild (i.e., minor) and severe (i.e., major) forms; the severity of the disease depends on the number and combination of genes affected. Because individuals with thalassemia minor variants have few physical symptoms and a normal lifespan is expected, HSCT is not considered an appropriate treatment option.

The severe form of this disease is known as beta thalassemia major, Cooley's anemia, thalassemia major or Mediterranean anemia. Thalassemia major requires frequent, lifelong blood cell transfusions and folate supplements; the effects of iron overload may damage the heart, liver and endocrine systems. Without treatment, children with the severe form of the disease usually do not live beyond early childhood; however, individuals with successfully treated thalassemia may live until their forties or beyond (National Heart, Lung, and Blood Institute [NHLBI], 2010c).

**Myeloablative Allogeneic HSCT:** Allogeneic HSCT is considered a potentially curative therapy for selected individuals with thalassemia major who have an appropriate donor (Holstein, 2011; National Institutes of Health [NIH], 2010c; Hongeng, 2006; Jaing, 2005). Data strongly suggest that the optimal timing of HSCT of an individual with a human leukocyte antigen (HLA)-identical sibling donor is at a very early age (Yesilipek, 2007).

HSCT is associated with a non-negligible risk of transplantation-related mortality and morbidity which must be taken into account, considering the relevant improvements achieved with conventional therapy (Locatelli, 2005). The outcome of allogeneic hematopoietic stem-cell transplantation (HSCT) using a human leukocyte antigen (HLA)-identical family donor is largely dependent on the age of the recipient as well as on pretransplant parameters reflecting the degree of organ damage from iron overload (Resnick, 2007). Results with HSCT are generally better if no iron overload or organ damage is present and the patient has received a minimal number of erythrocyte transfusions (Smiers, 2010).

For individuals with good-risk disease with an HLA-compatible sibling donor, the probability of disease-free survival (DFS) is 80–90%. In children who do not have liver disease and have received regular chelation therapy, the probability of survival with transfusion independence is over 90% (Holstein, 2011; La Nasa, 2005; Locatelli, 2005). Worse results have been obtained in high-risk individuals where the probability of DFS with transfusion independence after the allograft is approximately 58% (La Nasa, 2005). Adults with thalassemia have more advanced disease and treatment-related organ complications, mainly because of prolonged exposure to iron overload. Adults generally have a worse outcome than children; their probabilities of overall survival (OS) and thalassemia-free survival are 65%–66% and 62%–65%, respectively (Smiers, 2010, Locatelli, 2005).

### Summary

**Myeloablative Allogeneic HSCT for Thalassemia:** Although data are not robust, myeloablative allogeneic HSCT is potentially curative for thalassemia major and is an accepted treatment option for selected children and young adults.

There are scarce data in the published peer-reviewed scientific literature regarding the safety and effectiveness of myeloablative HSCT for the treatment of adults with thalassemia major. The role of this therapy has not yet been established for this indication.

**Non-Myeloablative Allogeneic HSCT:** It has been considered essential to administer full myeloablative conditioning regimens for transplantation to ablate the abnormal endogenous marrow. Disease recurrence and graft-versus-host disease continue to be a source of morbidity and mortality following this therapy. Non-myeloablative regimens remain under clinical evaluation, with short post-transplantation follow-up times.

Resnick et al. (2007) reported the results of a cohort of 20 patients who underwent reduced toxicity fludarabine-based conditioning followed by allogeneic HSCT using matched-related and unrelated donors. Median patient age was 5.6 years. With a median follow-up of 39 months, 16 of 20 patients had sustained engraftment and were transfusion independent. The overall survival and thalassemia-free survival were 100% and 80%, respectively, at a median follow-up of 39 months. Larger cohorts of patients and prospective clinical trials are required to confirm the benefits of this approach as a possible better alternative to the existing protocols.

Hongeng et al. (2004) reported on an 18 year-old female patient with beta-thalassemia who received non-myeloablative conditioning with an allogeneic HSCT using a haploidentical donor graft. The patient experienced multiple post-transplant complications which resolved with treatment. The patient achieved full chimerism at one month and maintained it at a follow-up of 18 months. The authors reported that the patient had good quality of life and no features of thalassemia post transplantation.

### Summary

#### **Non-Myeloablative HSCT for Thalassemia**

Data are lacking to support the effectiveness of non-myeloablative allogeneic HSCT for the treatment of thalassemia major. The ability to draw conclusions regarding improved health outcomes is limited by small patient populations, heterogeneous conditioning regimens, and study design.

#### **Contraindications**

Many factors affect the outcome of tissue transplantation; the selection process is designed to obtain the best result for each individual. Overall health, age, and disease stage are extremely important considerations in evaluating candidates. Relative contraindications to hematopoietic stem-cell transplantation (HSCT) include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)

- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal)
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- presence of human immunodeficiency virus OR an active form of any ONE of the following:
  - hepatitis B virus (HBV)
  - hepatitis C virus (HCV)
  - human T-cell lymphotropic virus (HTLV)-1
- Karnofsky rating < 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status > 2

**Professional Societies/Organizations**

**National Marrow Donor Program (NMDP):** The NMDP (2008) lists hemoglobinopathies, including sickle cell disease (SCD) and thalassemia major, as diseases which are treatable by allogeneic hematopoietic stem-cell transplantation (HSCT).

**National Heart, Lung and Blood Institute (NHLBI):** The NHLBI (2007) notes that bone marrow transplantation can be a very effective treatment for sickle cell anemia, but because of its risks, only some individuals can or should have this procedure. The NHLBI also noted that it is usually used only for younger individuals with severe sickle cell anemia, but the decision is made on a case-by-case basis. HSCT for SCD should be considered for children who experience significant, noninfectious complications caused by vaso-occlusion. For severely affected children who have human leukocyte antigen- (HLA) identical sibling donors, families should be informed about benefits, risks and treatment alternatives. Regarding thalassemia, the NHLBI (2008) notes that stem cell transplantation is the only treatment that can cure thalassemia; it is most successful in children.

**Summary**

The published peer-reviewed scientific literature supports the safety and effectiveness of myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of selected children and young adults with sickle cell disease (SCD) and thalassemia major.

There are insufficient data in the published peer-reviewed scientific literature to support the safety and effectiveness of myeloablative allogeneic HSCT for the treatment of adults with SCD or thalassemia major. Additionally, there is insufficient evidence to support the effectiveness of non-myeloablative allogeneic HSCT for the treatment of SCD and thalassemia major in children or adults. Although a subject of clinical study, the role of HSCT for these indications has not yet been established.

**Coding/Billing Information**

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

**Covered when medically necessary when used to report myeloablative allogeneic bone marrow or blood-derived stem cell procedures for sickle cell disease or thalassemia major in children or young adults:**

<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 <sup>†</sup>	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 of pre-and post-transplant care in the global definition

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
282.41-282.49	Thalassemias
282.60-282.69	Sickle-cell disease

**Experimental/Investigational/Unproven/Not Covered when used to report non-myeloablative allogeneic bone marrow or blood-derived stem cell procedures for sickle cell disease or thalassemia major in children or young adults:**

<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
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<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
282.41-282.49	Thalassemias
282.60-282.69	Sickle-cell disease

**Experimental/Investigational/Unproven/Not Covered when used to report bone marrow or blood-derived stem cell procedures for sickle cell disease or thalassemia major in adults:**

<b>CPT®*</b> <b>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
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<b>ICD-9-CM</b>	<b>Description</b>
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<b>Diagnosis Codes</b>	
282.41-282.49	Thalassemias
282.60-282.69	Sickle-cell disease

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

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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	7/15/2008	0464	Stem-Cell Transplant for Sickle Cell Disease and Thalassemia Major

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