Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Sickle Cell Disease and Thalassemia Major**

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Table of Contents

Hyperlink to Related Coverage Policies

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

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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], 2013; Chiu, 2005; Sickle Cell Disease Association of America [SCDAA], 2014).

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. Although considered a standard approach for the treatment of malignant disease, HSCT with the use of haploidentical donors remains a subject of ongoing clinical trials. There are limited data to support the safety and effectiveness of a haploidentical donor for the treatment of sickle cell disease or thalassemia major.

Sickle Cell Disease (SCD): 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, 2013). 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 children and young adults at risk for complications of the disease.

Myeloablative Allogeneic HSCT: Myeloablative allogeneic HSCT is the only potentially curative treatment option for selected individuals with sickle cell disease or thalassemia major (Novelli, 2011; Bhatia, 2008; Krishnamurti, 2008). 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. Patient selection criteria 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 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).

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).

Literature Review

Oringanje et al. (2013) performed a systematic review to determine whether stem-cell transplantation can improve survival, and prevent symptoms and complications associated with sickle cell disease. Data from randomized controlled and quasi-randomized studies were lacking; therefore, no conclusions could be made. The authors note that this systematic review identified the need for a multicenter randomized controlled trial assessing the benefits and possible risks of HSCT comparing sickle status and severity of disease in an individual with SCD.

However, several case series, retrospective reviews, and registry analyses have demonstrated improved overall- and event-free survival with allogeneic HSCT, primarily in children ≤18 years (Dallas, 2013; Bernauldin, 2007; Panepinto, 2007; Locatelli, 2005). Five and six-year probabilities of disease-free-(DFS), and overall survival (OS) were 85%–86%, and 93%–97%, respectively (Dallas, 2013; Novelli, 2011; Bernauldin, 2007; Panepinto, 2007). In the retrospective analysis by Dallas et al. (2013) involving 22 children with sickle cell disease who underwent an allogeneic HSCT, median follow-up was 9.0 years, with an OS of 93% and a recurrence/graft failure rate of 0%, for those using matched-related donors. For those undergoing haploidentical allogeneic HSCT, median follow-up was 7.4 years, with an OS of 75%, DFS of 38%, and disease recurrence of

38%. Although limited by uncontrolled study design and small patient numbers, data suggest an improved overall survival (OS) with allogeneic hematopoietic stem-cell transplantation (HSCT).

Summary of Myeloablative Allogeneic HSCT for Sickle Cell Disease (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 in the adult population and at this time the role of myeloablative allogeneic HSCT for has not been established for this indication.

Non-Myeloablative Allogeneic HSCT for SCD: 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 cause ablation of 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 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 while continuing to meet the objective of reduced toxicity.

Literature Review
Outcomes of several uncontrolled trials (total n=19) suggest that donor chimerism is possible in a majority of patients (Krishnamurti, 2008; Horwitz, 2007; Horan, 2005; Iannone, 2003). However, controlled clinical trial data are lacking, study populations are very limited, and effect on overall health outcomes is unknown.

Krishnamurti (2008) evaluated outcomes for seven patients (median age eight years) with severe SCD who underwent allogeneic HSCT with reduced-intensity conditioning. 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 were alive, off immunosuppression, and six of seven patients had 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, had normal blood counts and were 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, 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.

Summary of 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 promising and a subject of ongoing research, the role of nonmyeloablative conditioning and allogeneic HSCT 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], 2012).

Myeloablative Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT) for Thalassemia: Allogeneic HSCT is considered a potentially curative therapy for selected individuals with thalassemia major who have an appropriate donor (Holstein, 2011; 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 HSCT using an 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).

Literature Review
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 is approximately 58% when transfusion independence after the allograft is achieved (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 DFS are 65%–66% and 62%–65%, respectively (Smiers, 2010, Locatelli, 2005).

Summary of 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 for Thalassemia: There is insufficient evidence in the published, peer-reviewed scientific literature regarding the feasibility of using non-myeloablative preparative regimens for patients with thalassemia. It has been considered essential to administer full myeloablative conditioning regimens for transplantation to ablate the abnormal host bone 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.

Literature Review
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.

Summary of Non-Myeloablative HSCT for Thalassemia
Data are lacking to support the safety and 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 to Transplantation
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 (1996-2014) 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 (2002) notes that bone marrow transplantation may offer a cure for a small number of people with sickle cell anemia. 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. Regarding thalassemia, the NHLBI (2012) notes that stem cell transplantation is the only treatment that can cure thalassemia; only a small number of people who have severe thalassemias are able to find a good donor match and have the risky procedure.

Use Outside of the US: No relevant information.

Summary
Although data are limited, 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. Further, use of allogeneic HSCT for these indications is supported by several professional organizations.

However, 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. Patient study populations are small and do not allow the ability to determine if health outcomes are improved. Further, professional society/organization support are lacking in published consensus documents. Although a subject of clinical study, the role of HSCT for these indications has not yet been established.

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 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:

CPT®* Codes	**Description**
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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38242	Allogeneic lymphocyte infusions

HCPCS Codes	**Description**
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 of pre-and post-transplant care in the global definition

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