Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Central Nervous System Tumors**

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Hyperlink to Related Coverage Policies

Stem-Cell Transplantation for Neuroblastoma

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Coverage Policy

Cigna covers autologous hematopoietic stem-cell transplantation (HSCT) following high-dose chemotherapy as medically necessary for the treatment of EITHER of the following central nervous system tumors:

- primitive neuroectodermal tumor (PNET)
- previously untreated or recurrent medulloblastoma

For information on coverage of stem-cell transplantation for neuroblastoma, refer to the Cigna Coverage Policy Stem-Cell Transplantation for Neuroblastoma.

Cigna does not cover autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of ANY of the following central nervous system tumors because it is considered experimental, investigational or unproven (this list may not be all inclusive):

- astrocytoma
- brainstem glioma
- ependymoma
- oligodendroglioma

Cigna does not cover allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of central nervous system tumors because it is considered experimental, investigational or unproven.

General Background

Primary central nervous system (CNS) tumors are a diverse group of tumors originating in the brain or spinal cord. CNS tumors, develop from different cell types, form in different areas of the CNS and may have different prognoses and treatment in children compared with adults (American Cancer Society [ACS], 2010b). Tumor types include, but are not limited to medulloblastoma/primitive neuroectodermal tumors, astrocytoma, glioma, and ependymoma. CNS tumors are more common in children than adults and constitute the most common solid tumors of childhood. For most primary brain tumors in children, the optimal treatment regimens have not been determined. Overall, CNS tumors have a poor prognosis.

In both children and adults, tumor location and extent of spread play important roles in treatment and prognosis. Despite the use of multimodality treatment involving surgery, radiotherapy and chemotherapy, the cure rate remains low in high-risk histological types, and for individuals with residual, recurrent or disseminated disease. Systemic chemotherapy is generally less effective because of the blood-brain barrier, which prevents many chemotherapeutic agents from reaching the brain (National Cancer Institute [NCI], 2014[a, c]).

In an attempt to eradicate residual neoplastic cells and improve cure rate high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) has been investigated as a treatment option for selected individuals with certain high-risk CNS tumors.

Stem-Cell Transplantation
HSCT refers to transplantation of hematopoietic stem cells from a donor into a patient. HSCT can be either autologous (i.e., using the patient's own stem cells) or allogeneic (i.e., using stem cells from a donor).

Contraindications to Transplantation
Many factors affect the outcome of tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. 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
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Autologous HSCT: High-dose chemotherapy and autologous HSCT has been used as initial, as well as salvage therapy with a variety of CNS malignancies. Comparison of the effects of HSCT between treatment trials remains challenging given the heterogeneity of these tumors, use of different combinations of chemotherapy as well as radiation therapies, and varied patient selection (Ratko, 2012). Results vary based on the ability of each strategy to allow better penetration of the blood brain barrier and to increase the dose-response effect. Myeloablative therapy may initially delay, and later avoid the use of radiotherapy in infants and toddlers (Kadota, 2008). Due to disease characteristics, overall prognosis and rarity of individual tumor types randomized controlled trials are not feasible; however, several prospective case reports and retrospective analyses demonstrate improvements in disease-free and overall survival in selected patients.

On behalf of the Agency for Healthcare Research and Quality (AHRQ), Ratko et al. (2012) published narrative and systematic reviews evaluating the comparative benefits and harms of HSCT versus standard therapies or disease natural history in children with malignant solid tumors, including central nervous system (CNS) embryonal and glial tumors, inherited metabolic diseases, and autoimmune diseases. The authors noted evidence demonstrating benefit or harm of HSCT versus standard therapies or disease natural history was insufficient for most pediatric indications. The evidence for narrative review of central nervous system tumors included seven case series published since 2005; no randomized controlled trials (RCT), registry reports, or

clinical practice guidelines were identified in the literature search. Data suggest there is a favorable risk-benefit for HSCT in young children with high-risk or recurrent medulloblastoma. Data are limited regarding the use of this therapy for other childhood CNS embryonal tumors.

Systematic review addressed single and tandem autologous HSCT as initial therapy compared with conventional therapy and single autologous HSCT, respectively, for CNS embryonal tumors. Evidence included ten observational studies and two RCTs. Fifteen patients received tandem transplant and 132 patients received single HSCT. Based on the evidence it was not possible to clarify the role of single versus tandem procedure. There was also insufficient evidence to draw conclusions on overall survival with single HSCT compared to conventional therapy.

Systematic review also addressed single autologous HSCT as consolidation of high-risk, recurrent/refractory CNS glial tumors compared with conventional therapy. Evidence included one comparative cohort study of HSCT versus conventional therapy, one noncomparative cohort study, four RCTs, three Phase II trials, and 30 case series. Two hundred fifteen patients received hematopoietic stem-cell transplantation (HSCT); 797 received conventional therapy. Evidence was evaluated in five groups: anaplastic astrocytoma and glioblastoma multiforme (astrocytic tumors), choroid plexus tumor, ependymoma, and other glial tumor patients. Low strength evidence on overall survival suggests a benefit with single HSCT compared to conventional therapy for the treatment of high- risk recurrent or progressive anaplastic astrocytoma; however, the authors note the risk of bias is high and data are limited to only 17 patients. Data also suggested a harm of HSCT for overall survival for nonanaplastic mixed or unspecified ependymoma compared to conventional therapy. Evidence was insufficient to determine benefit of HSCT compared to conventional therapy for the treatment of high-risk newly diagnosed glioblastoma multiforme, newly diagnosed anaplastic, non anaplastic, mixed, or unspecified ependymoma, recurrent ependymoma, choroid plexus carcinoma, or other gliomas.

In a recent retrospective analysis of 18 consecutive children with primary (n=14) and recurrent (n=4) brain tumors Panosyan et al. (2011) reported three-year progression-free and overall survival probabilities of 60.5% and 69.3%, respectively. This data suggest that autologous HSCT may have a definitive role for selected patients with poor prognosis brain tumors.

Gill et al. (2008) performed a retrospective review comparing the results of adult patients (i.e. ≥18 years) with recurrent central nervous system tumors who received HSCT (n=10) or conventional-dose therapy (n=13). Of the patients undergoing transplantation (n=10) eight had a diagnosis of medulloblastoma; two patients were diagnosed with neuroblastoma. Six patients received tandem autologous HSCT; four patients received a single autologous HSCT. Transplantation was associated with increased survival (p=.044) compared with those receiving conventional chemotherapy. There was an improvement in time-to-progression for patients who received tandem versus a single dose of myeloablative chemotherapy (p=0.46); however, no improvement in survival was seen (p=0.132).

The safety and effectiveness of tandem high-dose chemotherapy and autologous transplantation for the treatment of CNS tumors is the subject of ongoing research. At this time it is still unknown whether the use of this therapy for patients with bulky residual tumor or for heavily pretreated patients will improve outcome compared with single-cycle myeloablative chemotherapy regimens (Marachelian, 2008).

Medulloblastoma/Primitive Neuroectodermal Tumor (PNET): In adults over age 45, 90% of brain tumors are gliomas, with over 77% of these being high-grade. Medulloblastoma and supratentorial primitive neuroectodermal tumor (sPNET) may be responsive to conventional chemotherapy; however, while 30–50% of patients will have objective response, long-term disease control with conventional therapy is rare.

Treatment options for individuals with medulloblastoma or primitive neuroectodermal tumors may include combination chemotherapy, systemic and oral chemotherapy plus intrathecal chemotherapy; higher-dose chemotherapy supported by autologous bone marrow rescue or peripheral stem cell rescue, and chemotherapy followed by radiation therapy to the primary tumor site (National Cancer Institute [NCI], 2014[d]). Especially in young children, high-dose chemotherapy to delay or avoid craniospinal radiotherapy has been recognized as part of a multimodal risk-adapted treatment strategy.

Literature Review

There are limited data from randomized controlled trials regarding the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for medulloblastoma or primitive neuroectodermal tumors (PNET). However, outcomes from several prospective trials, case series, and retrospective studies demonstrate improved response rates, and disease-free-, event-free- and/or overall survival with the use of high-dose chemotherapy and autologous HSCT for primary brain tumors, including medulloblastoma and PNET. Five-year overall survival (OS) rates range from 85–39%; event-free survival (EFS) ranged from 83%–49% (Dunkel, 2010; Chintagumpala, 2009; Grodman, 2009; Cheuk, 2008; Fangusaro, 2008a; Ridola, 2008; Sung, 2007; Gajiar, 2006, Chi, 2004).

Although data are not robust, improved response rates, and improved EFS and OS have been demonstrated in a number of uncontrolled prospective and retrospective studies. Autologous HSCT is considered an acceptable treatment option for this indication. Especially in young children, high-dose chemotherapy to delay or avoid craniospinal radiotherapy has been recognized as part of a multimodal treatment strategy.

Astrocytoma: High-grade astrocytic tumors (i.e., anaplastic astrocytomas and glioblastoma) are often locally invasive and extensive (National Cancer Institute [NCI, 2014e). Autologous HSCT has been proposed as a treatment for this indication.

Literature Review
Finlay et al. (2008) reported the results of a prospective, nonrandomized trial of 27 children and adolescents with glioblastoma multiforme (n=17), or anaplastic astrocytoma (n=10) who received myeloablative chemotherapy followed by autologous HSCT with one of three chemotherapy regimens following initial tumor progression. Event-free survival (EFS) and mortality rates following myeloablative chemotherapy for these patients was compared with outcomes of a cohort of similar patients who received conventional chemotherapy following initial tumor progression (n=56). Five of 27 children (two with glioblastoma multiforme and three with anaplastic astrocytoma) had an EFS of 8.3 to 13.3 years (median 11.1 years) following myeloablative therapy. No significant differences in overall survival (OS) were noted between the two groups when not stratified according to whether patients were surgically debulked prior to treatment (p=0.39). When patients were stratified according to surgical debulking, differences in survival were statistically significant (p=.017).

Although results are promising, the ability to draw conclusions regarding improved health outcomes with this therapy is limited by study design and small patient population. The role of HSCT for this indication has not yet been established.

Brainstem Glioma: In brainstem gliomas, the use of more aggressive chemotherapy strategies including high-dose chemotherapy followed by peripheral blood stem-cell reinfusion results in relatively brief-duration responses and few instances of significant tumor reduction lasting 12 months or longer (Dorsey, 2013).

Literature Review
Bay et al. (2007) reported the results of a retrospective study sponsored by the European Group for Blood and Marrow Transplantation. Two-hundred seventeen patients with high-grade supratentorial glioma underwent high-dose chemotherapy followed by autologous HSCT. The median age was 44.8 years. Treatment-related mortality was 4.5%. With a median follow-up of eight years, the median OS was 20 months. The survival probabilities at 6 months, 1, 5 and 10 years were 84%, 62%, 32%, and 17%, respectively. At the time of the study publication, the authors reported that only five patients (8%) were alive.

Data are limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for the treatment of glioma. The role of HSCT has not yet been established for this indication.

Ependymoma: There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for this indication. The role of this therapy has not yet been established for this indication.

Oligodendroglioma: There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for the treatment of oligodendroglioma. The role of this therapy has not yet been established for this indication.

Allogeneic HSCT: There are limited data in the published peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for the treatment of central nervous system (CNS) tumors. The role of allogeneic HSCT has not yet been established for this indication.

Professional Societies/Organizations
National Cancer Institute (NCI): The NCI has published comments regarding the use of high-dose chemotherapy with autologous stem-cell rescue for various central nervous system tumors:

- **Medulloblastoma:** According to the Childhood Central Nervous System Embryonal Tumors Treatment (PDQ®) (NCI, 2014d), standard treatment options for children ≤3 years with newly-diagnosed medulloblastoma in children continue to evolve and may include utilizing higher-dose chemotherapeutic regimens supported by autologous stem cell rescue or peripheral stem cell rescue. A variety of different treatment approaches are under evaluation for children >3 years with poor-risk medulloblastoma or pineoblastoma, including the use of higher doses of chemotherapy supported by autologous bone marrow rescue or peripheral stem cell rescue.

- **Primitive Neuroectodermal Tumor (PNET):** For children ≤ 3 years with newly diagnosed supratentorial PNET tumors and children >3 years with poor risk pineoblastoma, the Childhood Central Nervous System Embryonal Tumors Treatment (PDQ®) (NCI, 2014d) notes that treatment is similar to that outlined for the treatment of medulloblastoma. For children with recurrent PNET who have previously received radiation treatment the NCI notes higher-dose chemotherapy supported with autologous bone marrow rescue or peripheral stem cell support, have been used with variable results.

- **Adult Glioma /Oligodendroglioma**: The Adult Brain Tumors Treatment (PDQ®) (NCI, 2014a) does not mention HSCT as a treatment option for this indication.

- **Diffuse Intrinsic Pontine Glioma:** The Childhood Brain Stem Glioma Treatment (PDQ®) (NCI, 2014b) notes that high-dose, marrow-ablative chemotherapy with autologous hematopoietic stem cell rescue has been ineffective in extending survival in children.

- **High-Grade Childhood Recurrent Cerebral Astrocytoma:** The Childhood Astrocytomas Treatment (PDQ®) (National Cancer Institute [NCI], 2014[e]) notes HSCT may be effective in a subset of patients with minimal residual disease at time of recurrence; however, note that it is not considered standard therapy.

- **Ependymoma:** The NCI (2014g) notes there is no evidence that HSCT is of benefit.

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™): Regarding medulloblastoma and supratentorial primitive neuroectodermal tumor (PNET), the NCCN (2014) notes that autologous HSCT is a strategy for patients who have no evidence of disease following resection or conventional chemotherapy.

Use Outside of the US: No relevant information.

Summary
Despite the use of multimodal treatment, the prognosis of high-risk central nervous system (CNS) tumors remains poor with standard treatment options. Although the data are not robust, the published peer-reviewed scientific literature supports improved health outcomes with the use of autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of previously untreated or recurrent medulloblastoma and primitive neuroectodermal tumor (PNET). Data are lacking to support the safety and effectiveness of autologous HSCT for the treatment of astrocytoma, brainstem glioma, ependymoma, and oligodendroglioma or allogeneic HSCT for the treatment of central nervous system tumors. Further, consensus support in the form of published guidelines is lacking for the use of HSCT for these indications.

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 autologous bone marrow or blood-derived stem cell procedures for medulloblastoma/primitive neuroectodermal tumors (PNET):

CPT®* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
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
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell remover
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
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS Codes	Description
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

Experimental/Investigational/Unproven/Not Covered when used to report autologous bone marrow or blood-derived stem cell procedures for any other CNS tumors including astrocytoma, brainstem glioma, ependymoma, and oligodendroglioma:

CPT®* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
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
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell remover
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
38232	Bone marrow harvesting for transplantation; autologous

38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS Codes	Description
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

Experimental/Investigational/Unproven/Not Covered when used to report allogeneic bone marrow or blood-derived stem cell procedures for the treatment of central nervous system tumors:

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 remover
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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