Hematopoietic Stem-Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma

Policy #  00063
Original Effective Date:  01/28/2002
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider autologous hematopoietic stem-cell transplantation (HSCT) as consolidation therapy for previously untreated embryonal tumors of the central nervous system (CNS) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy to be eligible for coverage (See Note below).

Based on review of available data, the Company may consider autologous hematopoietic stem-cell transplantation (HSCT) to treat recurrent embryonal tumors of the central nervous system (CNS) to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Embryonal Tumors of the CNS
Based on review of available data, the Company considers tandem autologous hematopoietic stem-cell transplant (HSCT) to treat embryonal tumors of the central nervous system (CNS) to be investigational.*

Based on review of available data, the Company considers allogeneic hematopoietic stem-cell transplantation (HSCT) to treat embryonal tumors of the central nervous system (CNS) to be investigational.*

Ependymoma
Based on review of available data, the Company considers autologous, tandem autologous and allogeneic hematopoietic stem-cell transplant (HSCT) to treat ependymoma to be investigational.*

Note: In general, use of autologous hematopoietic stem-cell transplantation (HSCT) for previously untreated medulloblastoma has shown no survival benefit for those patients considered to be at average risk (i.e., patient age older than three years, without metastatic disease, and with total or near total surgical resection [≤ 1.5 cm² residual tumor]) when compared to conventional therapies.
Background/Overview
High-dose chemotherapy with HSCT has been investigated as a possible therapy in pediatric patients with brain tumors, particularly in patients with disease that is considered high risk. In addition, the use of HSCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous SCT) or from a donor (i.e., allogeneic SCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

Hematopoietic Stem-Cell Transplantation for Brain Tumors
Autologous HSCT allows for escalation of chemotherapy doses above those limited by myeloablation and has been tried in patients with high-risk brain tumors in an attempt to eradicate residual tumor cells and improve cure rates. The use of allogeneic HSCT for solid tumors does not rely on escalation of chemotherapy intensity and tumor reduction, but rather on a graft-versus-tumor effect. Allogeneic HSCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor or cannot be harvested.

Central Nervous System Embryonal Tumors
Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system embryonal tumors are more common in children and are the most common brain tumor in childhood. They are primarily composed of undifferentiated round cells, with divergent patterns of differentiation. It has been proposed that these tumors be merged under the term “primitive neuroectodermal tumor” (PNET), however, histologically similar tumors in different locations in the brain demonstrate different molecular genetic alterations. Embryonal tumors of the CNS include medulloblastoma, medulloepithelioma, supratentorial primitive neuroectodermal tumors (sPNETs) (pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymoblastoma, and atypical teratoid/rhabdoid tumor (AT/RT).

Medulloblastomas account for 20% of all childhood CNS tumors. The other types of embryonal tumors are rare by comparison. Surgical resection is the mainstay of therapy with the goal being gross total resection with adjuvant radiation therapy, as medulloblastomas are very radiosensitive. Treatment protocols are based on risk stratification, as average or high risk. The average-risk group includes children older than three years, without metastatic disease, and with tumors that are totally or near totally resected (< 1.5 cm² of residual disease). The high-risk group includes children aged 3 years or younger, or with metastatic disease, and/or subtotal resection (> 1.5 cm² of residual disease).

Current standard treatment regimens for average-risk medulloblastoma (postoperative craniospinal irradiation with boost to the posterior fossa followed by 12 months of chemotherapy) have resulted in five
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year overall survival (OS) rates of 80% or better. For high-risk medulloblastoma treated with conventional doses of chemotherapy and radiotherapy, the average event-free survival (EFS) at 5 years ranges from 34%–40% across studies. Fewer than 55% of children with high-risk disease survive longer than five years. The treatment of newly diagnosed medulloblastoma continues to evolve, and in children under the age of three, because of the concern of the deleterious effects of craniospinal radiation on the immature nervous system, therapeutic approaches have attempted to delay and sometimes avoid the use of radiation, and have included trials of higher-dose chemotherapeutic regimens with autologous HSCT.

Supratentorial PNETs are most commonly located in the cerebral cortex and pineal region. The prognosis for these tumors is worse than for medulloblastoma, despite identical therapies. After surgery, children are usually treated similarly to children with high-risk medulloblastoma. Three- to 5-year OS rates of 40%–50% have been reported, and for patients with disseminated disease, survival rates at five years range from 20%–30%.

Recurrent childhood CNS embryonal tumor is not uncommon, and depending on which type of treatment the patient initially received, autologous HSCT may be an option. For patients who receive high-dose chemotherapy and autologous HSCT for recurrent embryonal tumors, objective response is 50%–75%; however, long-term disease control is obtained in fewer than 30% of patients, and is seen primarily in patients in first relapse with localized disease at the time of relapse.

Ependymoma
Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually contiguous with the ventricular system. In children, the tumor typically arises intracranially, while in adults, a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the entire neuroaxis. Ependymomas are distinct from ependymoblastomas due to their more mature histologic differentiation. Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy usually does not play a role in the initial treatment of ependymoma. However, disease relapse is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional-dose chemotherapy, high-dose chemotherapy with autologous HSCT has been investigated as a possible salvage therapy.

Note: Other CNS tumors include astrocytoma, oligodendroglioma, and glioblastoma multiforme. However, these tumors arise from glial cells and not neuroepithelial cells.

Due to their neuroepithelial origin, peripheral neuroblastoma and Ewing’s sarcoma may be considered PNETs.
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Rationale/Source
Central Nervous System Embryonal Tumors
Newly diagnosed

Chintagumpala and colleagues reviewed EFS of 16 patients with newly diagnosed sPNET treated with risk-adapted craniospinal irradiation and subsequent high-dose chemotherapy with autologous HSCT between 1996 and 2003. Eight patients were considered at average risk and 8 were at high risk (defined as the presence of residual tumor larger than 1.5 cm² or disseminated disease in the neuroaxis). Median age at diagnosis was 7.9 years (range: 3–21 years). Seven patients had pineal PNET. After a median follow-up of 5.4 years, 12 patients were alive. Five-year EFS and OS for the patients with average risk disease was 75% (+/- 17%) and 88% (+/- 13%) and for the high-risk patients 60% (+/- 19%) and 58% (+/- 19%). No treatment-related toxicity deaths were reported. The authors concluded that high-dose chemotherapy with stem-cell support after risk-adapted craniospinal irradiation allows for a reduction in the dose of radiation needed to treat nonmetastatic, average-risk sPNET, without compromising EFS.

Fangusaro and colleagues reported outcomes for 43 children with newly diagnosed sPNET treated prospectively on 2 serial studies (Head Start 1 [HS1] and Head Start 2 [HS2]) between 1991 and 2002 with intensified induction chemotherapy followed by myeloablative chemotherapy and autologous HSCT. There were no statistical differences between HS1 and HS2 patient demographics. After maximal surgical resection, patients underwent induction chemotherapy. If, after induction, the disease remained stable or there was partial or complete response, patients underwent myeloablative chemotherapy with autologous HSCT (n = 32). Patients with progressive disease at the end of induction were not eligible for consolidation. Five-year EFS and OS were 39% (95% CI: 24–53) and 49% (95% CI: 33–62), respectively. Patients with nonpineal tumors did significantly better than patients with pineal PNETs (2-year and 5-year EFS of 57% vs. 23% and 48% vs. 15%, respectively and 2-year and 5-year OS of 70% vs. 31% and 60% vs. 23%, respectively). Sixty percent of survivors were alive without exposure to radiation therapy.

Dhall and colleagues reported outcomes for children younger than three years of age at diagnosis of nonmetastatic medulloblastoma, after being treated with five cycles of induction chemotherapy and subsequent myeloablative chemotherapy and autologous HSCT. Twenty of 21 children enrolled completed induction chemotherapy, of which 14 had a gross total surgical resection and 13 remained free of disease at the completion of induction chemotherapy. Of 7 patients with residual disease at the beginning of induction, all achieved a complete radiographic response to induction chemotherapy. Of the 20 patients who received consolidation chemotherapy, 18 remained free of disease at the end of consolidation. In patients with gross total tumor resection, 5-year EFS and OS were 64% (+/- 13) and 79% (+/- 11), respectively, and for patients with residual tumor, 29% (+/- 17) and 57% (+/- 19), respectively. There were 4 treatment-related deaths. The need for craniospinal irradiation was eliminated in 52% of the patients, and 71% of survivors avoided irradiation completely, with preservation of quality of life and intellectual functioning.

Gajjar and colleagues reported the results of risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and autologous HSCT in 134 children with newly diagnosed medulloblastoma. After tumor resection, patients were classified as having average-risk disease (n = 86), defined as ≤ 1.5 cm² residual tumor and no metastatic disease or high-risk disease (n = 48), defined as > 1.5 cm² residual disease or...
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metastatic disease localized to the neuroaxis. A total of 119 children completed the planned protocol. Five-year OS was 85% (95% CI: 75–94) among the average-risk cases and 70% (95% CI: 54–84) in the high-risk patients. Five-year EFS was 83% (95% CI: 73–93) and 70% (95% CI: 55–85) for average- and high-risk patients, respectively. No treatment-related deaths were reported.

Lee and colleagues retrospectively reviewed the medical records of 13 patients diagnosed with AT/RT who were treated at their institute at Seoul National Children's University Hospital (Korea). The median age was 12 months (range: 3–67 months), and 7 patients were younger than 1-year old at the time of diagnosis. Three patients (23%) underwent high-dose chemotherapy and autologous HSCT. The authors assessed the impact on OS in these 3 patients, as compared to the remaining 10 patients undergoing other chemotherapy regimens. No statistical difference in OS was observed between these 2 groups (p = 0.36); however, the median survival was reported to be higher in the HSCT group (15 months) compared to the non-HSCT group (9 months).

National Cancer Institute (NCI) Clinical Trial Database (PDQ®)

- A Phase III study of combination chemotherapy, radiation therapy, and an autologous peripheral blood stem-cell transplant in treating young patients with AT/RT (NCT00653068, COG-ACNS0333) is active. The primary purpose of this multi-center study (being undertaken in 88 trial sites across the U.S., Australia, and Canada) is to determine the EFS and OS of children (birth to 21 years of age) with AT/RT treated with surgery, high-dose chemotherapy combined with HSCT, and radiation therapy. Expected enrollment is 70 patients, with an estimated trial completion date of April 2014.

- A Phase III study of radiation therapy and combination chemotherapy followed by autologous stem-cell transplant in patients with newly diagnosed medulloblastoma, sPNET, or atypical teratoid/rhabdoid tumor (AT/RT) (NCT00085202, SJCRH-SJMB03) is active. The purpose of the study is to compare 2 different regimens of radiation therapy when given together with chemotherapy and autologous stem-cell transplant. Projected accrual is 413 patients, and estimated date of study completion is September 2018.

- A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiopeta and carboplatin with or without etoposide followed by autologous hematopoietic stem-cell rescue in pediatric patients with previously untreated malignant brain tumors (NCT00392886; CHLA-HEAD-START-III) is closed. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem-cell rescue. Expected enrollment was 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.

- A Phase III randomized study of intensive induction chemotherapy comprising vincristine, etoposide, cyclophosphamide, and cisplatin with or without high-dose methotrexate and leucovorin followed by consolidation chemotherapy comprising carboplatin and thiopeta and peripheral blood stem-cell rescue in pediatric patients with newly diagnosed sPNETs or high-risk medulloblastoma (NCT00336024, COG-ACNS0334) is active. The study was intended to compare the response rate of induction therapy with or without methotrexate and leucovorin. Expected enrollment is 96 patients, with an estimated trial completion date of September 2018.
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Recurrent

Raghuram and colleagues performed a systematic review of the literature regarding the outcome of patients with relapsed sPNET treated with high-dose chemotherapy and autologous HSCT. Eleven observational studies published before 2010 met their inclusion criteria; 4 of these were prospective case-series. The 11 studies consisted of 46 patients diagnosed with relapsed sPNET or pineoblastoma who received autologous HSCT for treatment of relapse. Of those, 15 patients were children younger than 3 years of age, and 15 were pineoblastomas. With a median follow-up of 40 months (range 3-123 months) 15 patients were reported alive. Thirteen patients (of 15 survivors) did not receive craniospinal irradiation. The 12-month OS rate of the cohort was 44.2 ± 7.5 months. Twelve-month OS for children younger than 36 months was 66.7 ± 12.2 months, while for older children, 12-month OS was 27.8 ± 10.6 (p = 0.003). Twelve-month OS was 20.0 ± 10.3 for those patients with pineoblastoma versus 54.6 ± 9.0 for those with non-pineal sPNETs (p < 0.001). Cox regression analysis revealed pineal location as the only independent adverse prognostic factor. Based on these pooled results, high-dose chemotherapy with HSCT might lead to survival primarily in younger children with relapsed sPNET, even in the absence of concomitant use of radiotherapy, whereas the outcome in older children and/or in a pineal location is poor with this modality.

In the earlier publication, Dunkel and colleagues reported the outcomes of 23 patients with recurrent medulloblastoma treated with high-dose carboplatin, thiopeta, and etoposide. Seven patients were event-free survivors at a median of 54 months, with OS estimated at 46% at 36 months. Hematopoietic stem-cell transplantation was expected to be most effective with minimal disease burden. Thus, Dunkel and colleagues suggested increased surveillance for recurrence or aggressive surgical debulking at the time of recurrence. The authors also acknowledged the potential for effects of patient selection bias on their results, since not all patients eligible for the protocol were enrolled.

Grodman et al. reported outcomes of eight patients with relapsed medulloblastoma with metastasis (n = 7) and relapsed germinoma (n = 1) who received dose-intensive chemotherapy with autologous HSCT. Mean age was 12.9 years (range: 5–27.8 years). Mean survival post-transplant was 4.8 years (range: 8–160+ months). The 2-year and 5-year OS rates were 75% and 50%, respectively.

Gill and colleagues reported outcomes for 23 adult patients (18 years or older) treated for recurrent embryonal CNS tumors between 1976 and 2004, comparing high-dose chemotherapy with autologous HSCT (n = 10) with an historic control group of patients treated with conventional-dose chemotherapy (n = 13). In the HSCT group, 6 patients received tandem autologous transplants. Autologous HSCT was associated with increased survival (p = 0.044) and a longer time to disease progression (TTP) (p = 0.028). Median TTP for the conventional versus HSCT group was 0.58 years and 1.25 years, respectively. Median survival was 2.00 years and 3.47 years, respectively. There were no long-term survivors in the conventional chemotherapy group. With a median follow-up of 2.9 years, five of the HSCT patients were alive, four without disease progression. In a comparison of outcomes between the patients who received a single versus tandem transplant, there was improvement in TTP favoring tandem transplant (p = 0.046), but no difference in survival was observed (p = 0.132).
Tandem Transplant
In 2013, Sung and colleagues reported the results of reduced-dose craniospinal radiotherapy followed by tandem double high-dose chemotherapy with autologous HSCT in 20 children older than 3 years of age with high-risk medulloblastoma (17 with metastatic disease and 3 having a postoperative residual tumor > 1.5 cm² without metastasis). The tumor relapsed/progressed in 4 patients, and 2 patients died of toxicity during the second transplant. Fourteen (70%) patients remained event-free at a median follow-up of 46 months (range, 23-82 months) from diagnosis. Late adverse effects evaluated at a median of 36 months (range, 12-68 months) after tandem HSCT included hypothyroidism, growth hormone deficiency, sex hormone deficiency, hearing loss, and renal tubulopathy.

In 2013, Friedrich and colleagues reported the results of double tandem high-dose chemotherapy with autologous HSCT in 3 children younger than 4 years of age with metastatic sPNET. These patients also received preventive craniospinal radiotherapy; they had residual disease before HSCT, but no evidence of disease after transplant (survival ranging from 2 to 10 years).

Park and colleagues reported the results of tandem double high-dose chemotherapy with autologous HSCT in 6 children younger than 3 years of age with newly diagnosed AT/RT. No treatment-related death occurred during the tandem procedure, and 5 (of 6) patients were alive at a median follow-up of 13 months (range 7-64) from first HSCT. Although 3 patients remained progression-free after tandem HSCT, the effectiveness of this modality is unclear because all survivors received radiotherapy, as well as tandem HSCT.

Sung and colleagues reported the results of a single or tandem double high-dose chemotherapy with autologous HSCT in 25 children with newly diagnosed high-risk or relapsed medulloblastoma or PNET following surgical resection. Three-year EFS for patients in complete remission (CR) or partial remission (PR) and less than PR at first high-dose chemotherapy was 67% or 16.7%, respectively. For 19 cases in CR or PR at first high-dose chemotherapy, 3-year EFS was 89% in the tandem double group and 44% in the single high-dose chemotherapy group, respectively. Four treatment-related deaths occurred, and in 4 of 8 young children, craniospinal radiotherapy was successfully withheld without relapse.

Allogeneic Transplant
The use of allogeneic HSCT for CNS embryonal tumors consists of rare case reports with mixed results.

National Cancer Institute Clinical Trial Database (PDQ)¹
No Phase III randomized trials using HSCT for recurrent embryonal CNS tumors are identified.

Ependymoma
Literature regarding autologous HSCT for the treatment of ependymoma primarily consists of small case series. Sung and colleagues reported the results of tandem double high-dose chemotherapy with autologous HSCT in 5 children younger than 3 years of age with newly diagnosed anaplastic ependymoma. All patients were alive at median follow-up of 45 months (range 31–62) from diagnosis, although tumor progressed at the primary site in one patient. No significant endocrine dysfunction occurred except for...
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hypothyroidism in one patient, and one patient had significant neurologic injury from primary surgical treatment. The results of this very small case series indicate that treatment with tandem HSCT is feasible in very young children with anaplastic ependymoma and that this strategy might also be a possible option to improve survival in these patients without unacceptable long-term toxicity. Further studies with larger patient cohorts are needed to confirm these results.

Mason and colleagues reported on a case series of 15 patients with recurrent ependymoma. Five patients died of treatment-related toxicities, 8 died from progressive disease, and 1 died of unrelated causes. After 25 months, 1 patient remains alive but with tumor recurrence. The authors concluded that their high-dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill and colleagues similarly reported a disappointing experience in 16 children treated with a thiotepa-based high-dose regimen.

A small series reported 5-year EFS of 12% (+/- 6%) and OS of 38% (+/- 10%) among 29 children younger than 10 years of age who received autologous HSCT following intensive induction chemotherapy to treat newly diagnosed ependymoma. Importantly, radiation-free survival was only 8% (+/- 5%) in these cases. The results of these series, although limited in size, further suggest HSCT is not superior to other previously reported chemotherapeutic approaches.

National Cancer Institute Clinical Trial Database (PDQ)
- A Phase III pilot study of induction chemotherapy followed by consolidation myeloablative chemotherapy comprising thiotepa and carboplatin with or without etoposide followed by autologous hematopoietic stem-cell rescue in pediatric patients with previously untreated malignant brain tumors, including ependymomas, (NCT00392886; CHLA-HEAD-START-III) is closed. The study compares 2 alternative induction regimens prior to myeloablative chemotherapy and stem-cell rescue. Expected enrollment was 120 patients, with an estimated trial completion date in December 2010. The publication date of this study is presently unknown.

Summary
Data from single-arm studies using autologous HSCT to treat newly diagnosed CNS embryonal tumors have shown an improved survival benefit (both event-free and overall), particularly in patients with disease that is considered high-risk. In addition, the use of autologous HSCT has allowed for a reduction in the dose of radiation needed to treat both average and high-risk disease, with preservation of quality of life and intellectual functioning, without compromising survival.

Data from single-arm studies using autologous HSCT to treat recurrent CNS embryonal tumors have shown improved survival benefit for some patients. The results from a 2012 systematic review of observational studies in patients with relapsed sPNET suggest that a sub-group of infants with chemo-sensitive disease might benefit from autologous HSCT, achieving survival without the use of radiation therapy, whereas the outcome in older children and/or in pineal location is poor with this modality.

More data on the use of tandem and allogeneic transplants for CNS embryonal tumors are needed.
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The use of HSCT for ependymoma has not shown a survival benefit compared to the use of conventional approaches, and the policy statement regarding ependymoma remains investigational.

References
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12/06/2001 Medical Policy Committee review
01/28/2002 Managed Care Advisory Council approval
05/07/2004 Medical Director review
05/18/2004 Medical Policy Committee review. Format revision. High-Dose Chemotherapy with Hematopoietic Stem-cell Support for Primitive Neuroectodermal policy developed separately from current HDC with Hematopoietic Stem-cell Support policy. No substance change to policy.
06/28/2004 Managed Care Advisory Council approval
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05/03/2005 Medical Director review
05/17/2005 Medical Policy Committee review. Patient Selection criteria added to policy.
05/23/2005 Managed Care Advisory Council approval
08/03/2005 Medical Director review
08/16/2005 Medical Policy Committee review. Coverage eligibility changes: autologous BMT to consolidate a remission after initial therapy in high-risk patients with PNETs, excluding medulloblastoma and ependymoma is considered to be eligible for coverage.
08/24/2005 Managed Care Advisory Council approval
07/12/2006 Medical Director review
07/19/2006 Medical Policy Committee review. Format changes. FDA information added. Additional rationale/source was added.
07/10/2007 Medical Director review
07/18/2007 Medical Policy Committee approval. Statement added to deny investigational when patient selection criteria is not met.
11/07/2007 Medical Director review
11/05/2008 Medical Director review
11/18/2008 Medical Policy Committee approval. Coverage eligibility unchanged
11/12/2009 Medical Policy Committee approval
11/04/2010 Medical Policy Committee review
11/16/2010 Medical Policy Implementation Committee approval. Policy title changed to remove “high-dose chemotherapy” and to change PNET to embryonal tumors. Policy statements reworded and separated to address ependymoma and embryonal CNS tumors specifically; however the intent of the policy remains the same.
11/03/2011 Medical Policy Committee approval
11/01/2012 Medical Policy Committee review
03/04/2013 Coding update
01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 01/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

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3. reference to federal regulations.

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A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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