



# 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.

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Coverage Policy Number ..... 6104

Subject **Temozolomide (Temodar®)**

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## Hyperlink to Related Coverage Policies

### 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers temozolomide (Temodar®) as medically necessary for treatment of adults (≥ 18 years old) with ANY of the following conditions:**

- anaplastic astrocytoma (i.e. disease progression on a drug regimen containing nitrosurea and procarbazine)
- anaplastic glioma
- brain metastasis if active against the primary tumor
- Ewing sarcoma
- glioblastoma multiforme (GBM) when used concomitantly with radiotherapy and then as maintenance treatment
- hemangiopericytoma
- islet cell tumors
- mesenchymal chondrosarcoma
- metastatic melanoma
- mycosis fungoides (MF)/Sezary syndrome (SS)
- primary central nervous system lymphoma
- soft tissue sarcoma of **EITHER** of the following areas:
  - extremity/trunk
  - retroperitoneal/ intra-abdominal area

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to temozolomide (Temodar<sup>®</sup>) therapy.

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## **FDA Approved Indications**

### **Newly Diagnosed Glioblastoma Multiforme**

Temodar is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

### **Refractory Anaplastic Astrocytoma**

Temodar is indicated for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

## **FDA Recommended Dosing**

### **High-Grade Glioma**

Temozolomide is administered orally at 75 mg/m<sup>2</sup>/day for 42 days concomitant with focal radiotherapy (60Gy administered in 30 fractions) followed by maintenance temozolomide for six cycles in patients with newly diagnosed high-grade glioma. The temozolomide dose should be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met:

- absolute neutrophil count  $\geq 1.5 \times 10^9$  /L
- platelet count  $\geq 100 \times 10^9$  /L
- common toxicity criteria (CTC) non-hematological toxicity  $\leq$  Grade 1 (except for alopecia, nausea and vomiting)

After the completion of concomitant phase for four weeks, temozolomide is administered for an additional six cycles of maintenance treatment which includes:

- Cycle 1: 150 mg/m<sup>2</sup>/day for five days followed by 23 days without treatment.
- Cycle 2–6: At the start of Cycle 2, the dose is escalated to 200 mg/m<sup>2</sup>, if the CTC non- hematologic toxicity for Cycle 1 is Grade  $\leq 2$  (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is  $\geq 1.5 \times 10^9$ /L, and the platelet count is  $\geq 100 \times 10^9$ /L. The dose remains at 200 mg/m<sup>2</sup> per day for the first five days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

The next cycle of temozolomide should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle.

### **Refractory Anaplastic Astrocytoma**

The starting dose of temozolomide is 150 mg/m<sup>2</sup>/day in patients with refractory anaplastic astrocytoma. The drug is given orally once daily for five consecutive days per 28-day treatment cycle. The dose is then adjusted based on the neutrophil and platelet counts. If the ANC and platelet count were above the acceptable limits at the time of the next cycle, the dose was increased to 200 mg/m<sup>2</sup>/day. If the ANC dropped below  $1 \times 10^9$ /L or platelet count was below  $50 \times 10^9$ /L, the dose of temozolomide should be decreased by 50 mg/m<sup>2</sup>, but not below 100 mg/m. The temozolomide-cyclic therapy should be given until disease progression or for a maximum of two years.

Dosage of temozolomide must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle.

Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is required for all patients receiving concomitant temozolomide and radiotherapy for the 42-day regimen. There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen.

As a single therapy, the dosing in patients with metastatic melanoma is given in a range of 150 to 200 mg/m<sup>2</sup> on days one to five of a 28-day treatment cycle.

## **Drug Availability**

### **Temodar Capsules**

Temodar capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths: 5 mg have opaque white bodies with green caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count; 20 mg have opaque white bodies with yellow caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count; 100 mg have opaque white bodies with pink caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count; 140 mg have opaque white bodies with blue caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count; 180 mg have opaque white bodies with orange caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count; 250 mg have opaque white bodies with white caps - the capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR". They are supplied in 5 count and 14 count. =

### **Temodar for Injection**

Temodar for injection is supplied in single-use glass vials containing 100 mg temozolomide. The lyophilized powder is white to light tan/light pink.

## **General Background**

### **Pharmacology**

Temozolomide is a pro-drug that does not require metabolic activation. The pharmacologic activity of temozolomide is due to the cytotoxic effects of the degradation product, 5-(3-methyltriazene-1-yl)imidazole-4-carboxamide (MTIC). MTIC blocks cellular replication by inhibition of deoxyribonucleic acid (DNA) methylation. Peak plasma concentrations are achieved within one hour after oral administration. Bioavailability is 96%. A high fat meal reduces peak plasma concentrations by 32%; the time to peak plasma concentrations are delayed by 1.15 hours and the extent of absorption by 9%. The pharmacokinetics of temozolomide are linear with dose. Temozolomide half-life is 1.5–1.8 hours. Clearance is 200–290 mL/min. Temozolomide and its metabolites are primarily excreted in the urine. Approximately 6% of the dose is excreted unchanged in the urine. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. Women have a 5% lower clearance than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

### **Guidelines**

The National Comprehensive Cancer Network (NCCN) recommends the following:

#### **Anaplastic Glioma**

##### **Grade 2A**

Consider as adjuvant treatment as a single agent or with deferred radiation therapy for anaplastic glioma. Treatment of recurrent disease or salvage therapy as a single agent or in combination with bevacizumab for anaplastic glioma

#### **Bone Cancer (Ewing sarcoma and Mesenchymal chondrosarcoma)**

##### **Grade 2A**

Used in combination with irinotecan with or without vincristine and growth factor support for relapse with or without radiation therapy progressive disease following primary treatment.

#### **Glioblastoma Multiforme**

##### **Grade 1**

Treatment following resection with or without carmustine polymer as concurrent and adjuvant treatment in combination with radiation therapy (RT) for patients with glioblastoma and good performance status (Karnofsky

Performance Status [KPS] 70 or greater) or chemotherapy with or without RT for patients with glioblastoma and poor performance status (KPS less than 70).

#### **Grade 2A**

Treatment of recurrent disease or salvage therapy as a single agent or in combination with bevacizumab for glioblastoma.

#### **Melanoma**

##### **Grade 2A**

Single agent or in combination with cisplatin and vinblastine with or without interleukin-2 and interferon alfa for unresectable stage III in-transit metastases; local, satellitosis, and/or intransit unresectable recurrence; incompletely resected nodal recurrence; limited recurrence or metastatic disease; disseminated recurrence or metastatic disease without brain metastases in patients with good performance status or disseminated recurrence with brain metastases in patients with good performance status.

#### **Metastatic Central Nervous System Lesions**

##### **Grade 2A**

Single-agent treatment for brain metastases if active against primary tumor (organ-specific therapy) consider as primary treatment for disseminated systemic disease with poor systemic treatment options (limited disease) consider for recurrent disease (limited disease) or for recurrent stable systemic disease (multiple lesions).

#### **NHL - Mycosis fungoides (MF)/Sezary syndrome (SS)**

##### **Grade 2A**

Second-line chemotherapy for patients with stage IA-IIA MF with histologic evidence of folliculotropic or large cell transformation or stage IIB with generalized extent tumor, transformed, and/or folliculotropic disease in combination with skin-directed therapy; stage IV non-Sezary or visceral disease; refractory or progressive stage III MF or SS.

#### **Pancreatic Endocrine Tumors (Islet Cell Tumors)**

##### **Grade 2A**

Management of unresectable locoregional disease and/or distant metastatic disease in patients with symptoms, clinically significant tumor burden, or clinically significant progression.

#### **Primary Central Nervous System Lymphoma**

##### **Grade 2A**

Treatment as a single agent or in combination with rituximab for progressive primary central nervous system lymphoma in patients who have received prior methotrexate-based regimen without prior radiation therapy after prolonged response to prior regimen or in combination with radiation therapy after short or no response to prior regimen.

Consider systemic treatment as a single agent or in combination with rituximab for progressive or recurrent primary central nervous system lymphoma in patients with prior whole brain radiation therapy.

#### **Refractory Anaplastic Astrocytoma**

##### **Grade 2A**

Treatment as a single agent for recurrent, progressive infiltrative supratentorial astrocytoma/oligodendroglioma.

#### **Soft Tissue Sarcoma**

##### **Grade 2A**

- **Retroperitoneal/ Intra-abdominal**  
Single agent for preoperative chemotherapy for resectable disease at initial presentation or for recurrent disease unresectable or metastatic disease at initial presentation or for progressive or recurrent disease
- **Hemangiopericytoma**  
In combination with bevacizumab for the treatment of solitary fibrous tumor and hemangiopericytoma.

- **Extremity/Trunk**

Single agent for preoperative chemotherapy or chemoradiation for stage II-III tumors (primary tumors or local recurrence); adjuvant chemotherapy or chemoradiation for resectable stage II-III disease (primary tumors or local recurrence); primary treatment as chemotherapy or chemoradiation for unresectable primary disease; adjuvant chemotherapy or chemoradiation for unresectable primary disease that becomes resectable following preoperative treatment; palliative chemotherapy for unresectable disease following primary treatment; primary treatment alone, or before or after metastasectomy with or without radiation therapy for single-organ confined, limited tumor bulk stage IV or recurrent disease that is amenable to complete resection; palliative chemotherapy for stage IV or recurrent disease with disseminated metastases; angiosarcoma.

### **Adverse Reactions/Contraindications**

Temozolomide is contraindicated in patients with a history of hypersensitivity to dacarbazine. Patients receiving immunosuppressive chemotherapy should not receive vaccination with live vaccines. The most frequently occurring adverse effects were nausea, vomiting, headache, and fatigue. Most adverse effects were self-limiting, and the nausea and vomiting were controlled with antiemetics. The incidence of grade 3 or 4 nausea occurred in 10%, and vomiting occurred in 6%.

The dose-limiting toxicity of temozolomide is myelosuppression. The median nadirs occurred at 28 days (range 1 to 44 days) for neutrophils and 26 days (range 22 to 40 days) for platelets. The myelosuppression is the most common dose-limiting adverse event. The average time for the absolute neutrophil count (ANC) and platelet count to return to normal from the nadir was 14 days.

The FDA Advisory Panel has stated temozolomide may induce hypercoagulability. Pulmonary emboli and venous thrombosis were observed in temozolomide clinical trials; however, it is possible those events may have been associated with the disease being treated rather than the treatment

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## **Coding/Billing Information**

**Note:** This section is not in use.

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## **References**

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2. Merck & Co., Inc. Temodar<sup>®</sup> (temozolomide) package insert (capsules and injection). Whitehouse Station, NJ: Merck & Co., Inc. Feb 2011.
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4. NCCN Drugs & Biologics Compendium<sup>™</sup>. Temodar<sup>®</sup> (temozolomide). Copyright 2011, National Comprehensive Cancer Network (NCCN).
5. Su YB, Sohn S, Krown SE, et al. Selective CD4<sup>+</sup> lymphopenia in melanoma patients treated with temozolomide: A toxicity with therapeutic implications. *J Clin Oncol* 22: 610-616, 2004.
6. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et.al. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;10:352(10):987-96.

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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	3/15/2008	6104	Temozolomide (Temodar®)
Great-West Healthcare	12/2007		Temodar

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