Clinical Policy: Temozolomide (Temodar)

Reference Number: CP.PHAR.77
Effective Date: 09/11
Last Review Date: 08/17

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for temozolomide (Temodar®).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Temodar (IV brand/PO brand and generic) is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Glioblastoma (must meet all):

1. Diagnosis of glioblastoma*:
2. Member meets a or b:
   a. FDA approved use:
      i. Adjuvant treatment following resection** (a or b):
         a) In combination with radiotherapy for up to 49 days;
         b) As a single agent for up to 6 total 28-day cycles post use with radiotherapy;
   b. Off-label NCCN recommended use (i or ii):
      i. Adjuvant treatment following resection**:
         a) As a single agent if tumor is positive for methylguanine methyltransferase (MGMT) gene promoter methylation†;
      ii. Treatment of recurrent disease (a or b):
         a) As a single agent;
         b) In combination with bevacizumab;
3. Prescribed dose does not exceed 200 mg/m^2/day.

**A high-grade WHO grade IV glioma also known as glioblastoma multiforme (GBM).*
***Resection may include total/subtotal resection or open/stereotactic biopsy.*
†MGMT is a DNA repair enzyme that can cause resistance to DNA-alkylating drugs including Temodar. Methylation of the promoter region on the gene encoding for MGMT silences the enzyme leading to enhanced tumor chemosensitivity. Promoter methylation is detectable by PCR or pyrosequencing.

Approval duration: 6 months

B. Anaplastic Astrocytoma (must meet all):

1. Diagnosis of anaplastic astrocytoma*;
2. Member meets a or b:
   a. FDA approved use:

i. Treatment of disease that has progressed on a drug regimen containing nitrosourea or procarbazine;

b. Off-label NCCN recommended use (i or ii):
   i. Adjuvant treatment after resection** for disease with 1p/19q uni- or non-deletion† (a or b):
      a) In combination with radiotherapy;
      b) As a single agent;
   ii. Treatment of recurrent disease (a or b):
      a) As a single agent;
      b) In combination with bevacizumab.

3. Prescribed dose does not exceed 200 mg/m2/day.

**A high-grade WHO grade III glioma.*
***Resection may include total/subtotal resection or open/stereotactic biopsy.*
†A 1p/19q uni- or non-deletion indicates a loss of chromosomal arms 1p or 19q, or loss of neither but not both. Deletions are detectable by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR).

Approval duration: 6 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

1. Uses outlined in the NCCN compendium and which meet NCCN categories 1 or 2a are covered for the following indications:
   a. Bone cancer:
      i. Ewing sarcoma;
   b. Central nervous system (CNS) cancers:
      i. Adult intracranial and spinal ependymoma (excluding subependymoma);
      ii. Adult low-grade infiltrative supratentorial astrocytoma/oligodendroglioma (excluding pilocytic astrocytoma);
      iii. Adult medulloblastoma and supratentorial primitive neuroectodermal tumors;
      iv. Brain metastases if Temodar was active against the primary tumor;
      v. Primary CNS lymphoma;
   c. Melanoma;
   d. Neuroendocrine tumors:
      i. GI tract, lung, thymus, pancreas;
      ii. Pheochromocytoma/paraganglioma;
   e. Non-Hodgkin's lymphomas
      i. Mycosis fungoides;
      ii. Sezary syndrome;
   f. Non-melanoma skin cancers:
      i. Dermatofibrosarcoma protuberans;
   g. Small cell lung cancer;
   h. Soft tissue sarcoma:
      i. Angiosarcoma;
      ii. Retroperitoneal/intra-abdominal;
      iii. Rhabdomyosarcoma;
      iv. Solitary fibrous tumor/hemangiopericytoma;

v. Extremity/superficial trunk, head/neck;

i. Uterine neoplasms:

i. Uterine sarcoma.

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy (e.g., no disease progression or unacceptable toxicity);
3. Prescribed dose does not exceed 200 mg/m^2/day.

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

Temodar contains temozolomide, an imidazotetrazine derivative. Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

Formulations:

Intravenous reconstituted solution*:

- Temodar: 100 mg

Oral capsules*:

- Temodar 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg
- Generic: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg

**The recommended dose for Temodar as an IV infusion over 90 minutes is the same as the dose for the Temodar oral capsule formulation.*

FDA Approved Indications:

Temodar is an alkylating (methylating) drug/oral capsule and IV formulation indicated for:

- Newly diagnosed glioblastoma multiforme
  - Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.
- Refractory anaplastic astrocytoma

- Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

Appendices

Appendix A: Abbreviation Key

CNS: central nervous system
FISH: fluorescence in situ hybridization
GBM: glioblastoma multiforme
MGMT: methylguanine methyl-transferase
MTIC: 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide
PCR: polymerase chain reaction
WHO: World Health Organization

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J8700	Temozolomide, oral, 5 mg
J9328	Injection, temozolomide, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Removed question about prior hypersensitivity reactions to dacarbazine Added a re-auth question specific to Centene benefits to allow bypassing the diagnosis questions. Replaced language about continuing benefits with the question inquiring about disease progression and unacceptable toxicity.	08/13	08/13
Added efficacy and safety data for Temodar Added Appendices A, B, C Algorithm: added initial criteria for Temodar for GBM, pneumocystitis pneumonia question, and approval period for 42 days Algorithm: split original algorithm into two separate figures (GBM and Anaplastic astrocytoma), and added 6 cycles to approval period of Temodar in GBM	08/14	08/14
Removed efficacy and related reference from background. Updated safety section and added related questions to both algorithms. Appendix A: abbreviations maintained Appendices B and C: criteria for initiation and criteria for dosing respectively are edited to Appendix B: when to initiate Temodar therapy, and Appendix C: when to discontinue Temodar therapy	08/15	08/15
Policy converted to new template. CBC, LFT, HBV screening requirements removed. Evidence of HBV infection removed as reason to discontinue; remaining reasons to discontinue are separated per indication.	07/16	08/16

Reviews, Revisions, and Approvals	Date	Approval Date
Glioblastoma: Toxicity criteria is restricted to continuation of therapy – footnote added defining Grades 3 and 4. Approved number of FDA labeled adjuvant cycles (after Temodar/radiotherapy) is increased from 6 to 12 cycles total. "No disease progression" is added under continuation criteria. All NCCN compendial uses added; NCCN glioblastoma and anaplastic astrocytoma criteria are outlined in section I. Initial policy approval periods are increased to 6 months.		
Glioblastoma adjuvant treatment for 12 cycles post radiotherapy is decreased to 6 cycles. Maximum dose added for both indications. Off-label coverage is limited to NCCN uses categorized as 1 or 2a (2b is removed). For anaplastic astrocytoma: Off-label use as a single agent is limited to positive identification of 1p19q uni- or non-deleted tumor status. Safety information is removed. Renewal periods are increased from 6 to 12 months. HCPCS codes updated	07/17	08/17
Typo fixed to allow coverage for anaplastic astrocytoma to match FDA approved indication for the treatment of disease that has progressed on a drug regimen containing nitrosourea or procarbazine. Previous policy indicated indicated use in disease that has progressed on nitrosourea and procarbazine	12/17	

References

1. Temodar Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; April 2017. Available at https://www.merck.com/product/usa/pi_circulars/t/temodar_capsules/temodar_pi.pdf. Accessed July 5, 2017.
2. Temozolomide. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed July 5, 2017.
3. Temozolomide: Drug information. In: UpToDate (Lexicomp), Waltham, MA: Walters Kluwer Health; 2017. Available at uptodate.com. Accessed July 5, 2016.
4. Central nervous system cancers (Version 1.2016). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed July 5, 2017.
5. Louis DN, Schiff D, Batchelor T. Classification and pathologic diagnosis of gliomas. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2017. Available at uptodate.com. Accessed July 6, 2017.
6. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathologica.* June 2016; 131(6): 803-820.
7. Shih HA, Batchelor T. Adjuvant radiation therapy for high-grade gliomas. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2017. Available at uptodate.com. Accessed July 7, 2017.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of

medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.