Temozolomide: Drug information

(For additional information see "Temozolomide: Patient drug information" and see "Temozolomide: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Temodar

Brand Names: Canada

ACH-Temozolomide; ACT Temozolomide; Temodal

Pharmacologic Category

Antineoplastic Agent, Alkylating Agent (Triazene)

Dosing: Adult

Note: Temozolomide is associated with a moderate emetic potential (Roila 2010); antiemetics are recommended to prevent nausea and vomiting. Prior to dosing, ANC should be ≥1,500/mm^3 and platelets ≥100,000/mm^3.

Anaplastic astrocytoma (refractory): Oral, IV: Initial dose: 150 mg/m^2 once daily for 5 consecutive days of a 28-day treatment cycle. If ANC ≥1,500/mm^3 and platelets ≥100,000/mm^3, on day 1 of subsequent cycles, may increase to 200 mg/m^2 once daily for 5 consecutive days of a 28-day treatment cycle. May continue until disease progression.

Dosage modification for toxicity:

ANC <1,000/mm^3 or platelets <50,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1,500/mm^3 and platelets >100,000/mm^3; reduce dose by 50 mg/m^2/day (but not below 100 mg/m^2) for subsequent cycle

ANC 1,000 to 1,500/mm^3 or platelets 50,000-100,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1,500/mm^3 and platelets >100,000/mm^3; maintain initial dose

Glioblastoma multiforme (newly diagnosed, high-grade glioma): Oral, IV:

Concomitant phase: 75 mg/m^2 once daily for 42 days with focal radiotherapy (60 Gy administered in 30 fractions). **Note:** PCP prophylaxis is required during concomitant phase and should continue in patients who develop lymphocytopenia until lymphocyte recovery to ≤grade 1. Obtain weekly CBC.

Continue at 75 mg/m^2 once daily throughout the 42-day concomitant phase (up to 49 days) as long as ANC ≥1,500/mm^3, platelet count ≥100,000/mm^3, and nonhematologic toxicity ≤grade 1 (excludes alopecia, nausea/vomiting)

Dosage modification for toxicity:

ANC ≥500/mm^3 but <1,500/mm^3 **or** platelet count ≥10,000/mm^3 but <100,000/mm^3 **or**

grade 2 nonhematologic toxicity (excludes alopecia, nausea/vomiting): Interrupt therapy

ANC <500/mm^3 **or** platelet count <10,000/mm^3 **or** grade 3/4 nonhematologic toxicity (excludes alopecia, nausea/vomiting): Discontinue therapy

Maintenance phase (consists of 6 treatment cycles): Begin 4 weeks after concomitant phase completion. **Note:** Each subsequent cycle is 28 days (consisting of 5 days of drug treatment followed by 23 days without treatment). Draw CBC on day 22 (or within 48 hours of day 22); hold next cycle and do weekly CBC until ANC >1,500/mm^3 and platelet count >100,000/mm^3; dosing modification should be based on lowest blood counts and worst nonhematologic toxicity during the previous cycle.

Cycle 1: 150 mg/m^2 once daily for 5 days of a 28-day treatment cycle

Cycles 2 to 6: May increase to 200 mg/m^2 once daily for 5 days; repeat every 28 days (if ANC ≥1,500/mm^3, platelets ≥100,000/mm^3 and nonhematologic toxicities for cycle 1 are ≤grade 2 [excludes alopecia, nausea/vomiting]); **Note:** If dose was not escalated at the onset of cycle 2, do not increase for cycles 3 to 6)

Dosage modification (during maintenance phase) for toxicity:

ANC <1,000/mm^3, platelet count <50,000/mm^3, or grade 3 nonhematologic toxicity (excludes alopecia, nausea/vomiting) during previous cycle: Decrease dose by 1 dose level (by 50 mg/m^2/day for 5 days), unless dose has already been lowered to 100 mg/m^2/day, then discontinue therapy.

If dose reduction <100 mg/m^2/day is required or grade 4 nonhematologic toxicity (excludes alopecia, nausea/vomiting), or if the same grade 3 nonhematologic toxicity occurs after dose reduction: Discontinue therapy

Cutaneous T-cell lymphoma, advanced (mycosis fungoides [MF] and Sézary syndrome [SS]; off-label use): Oral: 200 mg/m^2 once daily for 5 days every 28 days for up to 1 year (Querfeld 2011)

Ewing's sarcoma, recurrent or progressive (off-label use): Oral: 100 mg/m^2/dose days 1 to 5 every 21 days (in combination with irinotecan) (Casey 2009). Additional data may be necessary to further define the role of temozolomide in this condition

Glioblastoma multiforme (recurrent glioma) (off-label use): Oral: 200 mg/m^2 once daily for 5 days every 28 days; if previously treated with chemotherapy, initiate at 150 mg/m^2 once daily for 5 days every 28 days and increase to 200 mg/m^2 once daily for 5 days every 28 days with cycle 2 if no hematologic toxicity (Brada 2001; Yung 2000)

Melanoma, advanced or metastatic (off-label use): Oral: 200 mg/m^2 once daily for 5 days every 28 days (for up to 12 cycles). For subsequent cycles reduce dose to 75% of the original dose for grade 3/4 hematologic toxicity and reduce the dose to 50% of the original dose for grade 3/4 nonhematologic toxicity (Middleton 2000).

Neuroendocrine tumors, advanced (off-label use): Oral: 150 mg/m^2 once daily for 7 days every 14 days (in combination with thalidomide) until disease progression (Kulke 2006) **or** 200 mg/m^2 once daily (at bedtime) days 10 to 14 of a 28-day treatment cycle (in combination with capecitabine) (Strosberg 2011)

Primary CNS lymphoma, refractory (off-label use): Oral: 150 mg/m^2 once daily for 5 days every 28

days, initially in combination with rituximab (for 4 cycles), followed by temozolomide monotherapy: 150 mg/m^2 once daily for 5 days every 28 days for 8 cycles (Wong 2004) **or** 150 mg/m^2 once daily on days 1 to 7 and 15 to 21 every 28 days (initially in combination with rituximab for 1 or 2 cycles), followed by temozolomide maintenance monotherapy: 150 mg/m^2 once daily for 5 days every 28 days (Enting 2004). However, additional data may be necessary to further define the role of temozolomide in this condition.

Soft tissue sarcoma (off-label use): Oral:

Soft tissue sarcoma, metastatic or unresectable: 75 mg/m^2 once daily for 6 weeks (Garcia del Muro 2005)

Hemangiopericytoma/solitary fibrous tumor: 150 mg/m^2 once daily days 1 to 7 and days 15 to 21 of a 28-day treatment cycle (in combination with bevacizumab) (Park 2011). Additional data may be necessary to further define the role of temozolomide in this condition

Dosing: Pediatric

(For additional information see "Temozolomide: Pediatric drug information")

Note: Temozolomide is associated with a moderate emetic potential (Dupuis 2011); antiemetics are recommended to prevent nausea and vomiting.

Ewing's sarcoma, recurrent or progressive (off-label use): Children and Adolescents: Oral: Refer to adult dosing.

Neuroblastoma, relapsed or refractory (off-label use):

Children and Adolescents: Oral: 100 mg/m^2/dose days 1 to 5 every 21 days (in combination with irinotecan) for up to 6 cycles (Bagatell 2011)

Children ≥6 months and Adolescents: Oral: 150 mg/m^2/dose days 1 to 5 every 28 days (in combination with topotecan) until disease progression or unacceptable toxicity (Di Giannatale 2014)

Dosing: Geriatric

Refer to adult dosing. **Note:** Patients ≥70 years of age in the anaplastic astrocytoma study had a higher incidence of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than patients <70 years of age.

Dosing: Renal Impairment

Oral:

CrCl ≥36 mL/minute/m^2: There are no dosage adjustments provided in the manufacturer's labeling; however, dosage adjustment is not likely needed as no effect on temozolomide clearance was demonstrated.

Severe renal impairment (CrCl <36 mL/minute/m^2): There are no dosage adjustments provided in the manufacturer's labeling; use with caution (has not been studied).

Dialysis patients: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

Mild to moderate impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, pharmacokinetics are similar to patients with normal hepatic function.

Severe hepatic impairment: There are no dosage adjustments provided in the manufacturer's labeling; use with caution (has not been studied).

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, Oral:

Temodar: 5 mg [contains fd&c blue #2 (indigotine)]

Temodar: 20 mg, 100 mg

Temodar: 140 mg [contains fd&c blue #2 (indigotine)]

Temodar: 180 mg, 250 mg

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

Solution Reconstituted, Intravenous:

Temodar: 100 mg (1 ea) [pyrogen free; contains polysorbate 80]

Generic Equivalent Available (US)

May be product dependent

Administration

Temozolomide is associated with a moderate emetic potential (Dupuis 2011; Roila 2010); antiemetics are recommended to prevent nausea and vomiting.

Oral: Swallow capsules whole with a glass of water. Absorption is affected by food; therefore, administer consistently either with food or without food (was administered in studies under fasting and nonfasting conditions). May administer on an empty stomach and/or at bedtime to reduce nausea and vomiting. Do not repeat dose if vomiting occurs after dose is administered; wait until the next scheduled dose. Do not open or chew capsules; avoid contact with skin or mucous membranes if capsules are accidentally opened or damaged.

IV: Infuse over 90 minutes. Flush line before and after administration. May be administered through the same IV line as sodium chloride 0.9%; do not administer other medications through the same IV line.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be

worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration. For IV preparation, double gloves, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) are recommended. Double gloving, a gown, and (if dosage form allows) CSTDs are required during IV administration (NIOSH 2016).

Use

Anaplastic astrocytoma: Treatment of refractory anaplastic astrocytoma (refractory to a regimen containing a nitrosourea and procarbazine)

Glioblastoma multiforme: Treatment of newly-diagnosed glioblastoma multiforme (initially in combination with radiotherapy, then as maintenance treatment)

Use: Off-Label

Cutaneous T-cell lymphomas, advanced (mycosis fungoides [MF] and Sézary syndrome [SS]; Ewing's sarcoma (recurrent or progressive); Glioblastoma multiforme, recurrent; Melanoma, advanced or metastatic; Neuroblastoma (pediatric); Neuroendocrine tumors, advanced (carcinoid or islet cell); Primary CNS lymphoma, refractory; Soft tissue sarcomas, extremity/retroperitoneal/intra-abdominal:; Soft tissue sarcomas, hemangiopericytoma/solitary fibrous tumor; Anaplastic oligodendroglioma; Low-grade astrocytoma; Low-grade oligodendroglioma; Metastatic CNS lesions

Medication Safety Issues

Sound-alike/look-alike issues:

Temodar may be confused with Tambocor

Temozolomide may be confused with temsirolimus

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

Note: With CNS malignancies, it may be difficult to distinguish between CNS adverse events caused by temozolomide versus the effects of progressive disease.

>10%:

Cardiovascular: Peripheral edema (11%)

Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), convulsions (6% to 23%), hemiparesis (18%), dizziness (5% to 12%), ataxia (8% to 11%)

Dermatologic: Alopecia (55%), skin rash (8% to 13%)

Gastrointestinal: Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)

Hematologic & oncologic: Lymphocytopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%; children: 25%), neutropenia (grades 3/4: adults: 8% to 14%; children: 20%), leukopenia (grades 3/4: 11%)

Infection: Viral infection (11%)

Neuromuscular & skeletal: Weakness (7% to 13%)

Miscellaneous: Fever (13%)

1% to 10%:

Central nervous system: Amnesia (10%), insomnia (4% to 10%), drowsiness (9%), paresthesia (9%), paresis (8%), anxiety (7%), memory impairment (7%), abnormal gait (6%), depression (6%), confusion (5%)

Dermatologic: Pruritus (5% to 8%), xeroderma (5%), erythema (1%)

Endocrine & metabolic: Hypercorticoidism (8%), weight gain (5%)

Gastrointestinal: Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), dysgeusia (5%)

Genitourinary: Urinary incontinence (8%), urinary tract infection (8%), mastalgia (females 6%), urinary frequency (6%)

Hematologic & oncologic: Anemia (grades 3/4: 4%)

Hypersensitivity: Hypersensitivity reaction (≤3%)

Neuromuscular & skeletal: Back pain (8%), arthralgia (6%), myalgia (5%)

Ophthalmic: Blurred vision (5% to 8%), diplopia (5%), visual disturbance (visual deficit/vision changes 5%)

Respiratory: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)

Miscellaneous: Radiation injury (2% maintenance phase after radiotherapy)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Agitation, anaphylaxis, apathy, aplastic anemia, cholestasis, cytomegalovirus disease (primary and reactivation), diabetes insipidus, emotional lability, erythema multiforme, febrile neutropenia, flu-like symptoms, hallucination, hematoma, hemorrhage, hepatitis, hepatitis B (reactivation), hepatotoxicity, herpes simplex infection, herpes zoster, hyperbilirubinemia, hyperglycemia, hypersensitivity pneumonitis, hypokalemia, increased serum alkaline phosphatase, increased serum transaminases, injection site reaction (erythema, irritation,

pain, pruritus, swelling, warmth), interstitial pneumonitis, metastases (including myeloid leukemia), myelodysplastic syndrome, neuropathy, opportunistic infection (including pneumocystosis), oral candidiasis, pancytopenia (may be prolonged), peripheral neuropathy, petechia, pneumonitis, pulmonary fibrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, weight loss

Contraindications

Hypersensitivity (eg, allergic reaction, anaphylaxis, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis) to temozolomide or any component of the formulation; hypersensitivity to dacarbazine (both drugs are metabolized to MTIC)

Canadian labeling: Additional contraindications (not in U.S. labeling): Not recommended in patients with severe myelosuppression

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Myelosuppression may occur; may require treatment interruption, dose reduction and/or discontinuation; monitor blood counts. An increased incidence has been reported in geriatric and female patients. Prolonged pancytopenia resulting in aplastic anemia has been reported (may be fatal); concurrent use of temozolomide with medications associated with aplastic anemia (eg, carbamazepine, co-trimoxazole, phenytoin) may obscure assessment for development of aplastic anemia. ANC should be ≥1,500/mm^3 and platelets ≥100,000/mm^3 prior to treatment.

• Gastrointestinal toxicity: Temozolomide is associated with a moderate emetic potential (Dupuis 2011; Roila 2010); antiemetics are recommended to prevent nausea and vomiting.

• Hepatotoxicity: Hepatotoxicity has been reported; may be severe or fatal. Monitor liver function tests at baseline, halfway through the first cycle, prior to each subsequent cycle, and at ~2 to 4 weeks after the last dose. Postmarketing reports of hepatotoxicity have included liver function abnormalities, hepatitis, hepatic failure, cholestasis, hepatitis cholestasis, jaundice, cholelithiasis, hepatic steatosis, hepatic necrosis, hepatic lesion, and hepatic encephalopathy (Sarganas 2012).

• Pneumonia: *Pneumocystis jirovecii* pneumonia (PCP) may occur; risk is increased in those receiving steroids or longer dosing regimens. Monitor all patients for development of PCP (particularly if also receiving corticosteroids). PCP prophylaxis is required in patients receiving radiotherapy in combination with the 42-day temozolomide regimen.

• Secondary malignancies: Rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been reported.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with severe hepatic impairment.

• Renal impairment: Use with caution in patients with severe renal impairment; has not been studied in dialysis patients.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency

adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Dosage form specific issues:

• Polysorbate 80: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals (Isaksson 2002; Lucente 2000; Shelley 1995). Thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates after receiving parenteral products containing polysorbate 80 (Alade 1986; CDC 1984). See manufacturer's labeling.

Other warnings/precautions:

• Infusion time: Bioequivalence has only been established when IV temozolomide is administered over 90 minutes; shorter or longer infusion times may result in suboptimal dosing.

• Temozolomide resistance: Increased MGMT (O-6-methylguanine-DNA methyltransferase) activity/levels within tumor tissue is associated with temozolomide resistance. Glioblastoma patients with decreased levels (due to methylated MGMT promoter) may be more likely to benefit from the combination of radiation therapy and temozolomide (Hegi 2008; Stupp 2009). Determination of MGMT status may be predictive for response to alkylating agents.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider*

therapy modification

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Valproate Products: May enhance the adverse/toxic effect of Temozolomide. Valproate Products may increase the serum concentration of Temozolomide. *Risk C: Monitor therapy*

Food Interactions Food reduces rate and extent of absorption. Management: Administer consistently either with food or without food (was administered in studies under fasting and nonfasting conditions).

Pregnancy Risk Factor D (show table)

Pregnancy Implications Adverse events were observed in animal reproduction studies. May cause fetal harm when administered to pregnant women. Male and female patients should avoid pregnancy while receiving temozolomide.

Breast-Feeding Considerations It is not known if temozolomide is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

Dietary Considerations The incidence of nausea/vomiting is decreased when taken on an empty stomach. Take capsules consistently either with food or without food (absorption is affected by food).

Monitoring Parameters CBC with differential and platelets (prior to each cycle; weekly during glioma concomitant phase treatment; at or within 48 hours of day 22 and weekly until ANC >1,500/mm^3 and platelets >100,000/mm^3 for glioma maintenance and astrocytoma treatment). Monitor liver function tests at baseline, halfway through the first cycle, prior to each subsequent cycle, and at ~2 to 4 weeks after the last dose.

Mechanism of Action Temozolomide is a prodrug which is rapidly and nonenzymatically converted to the active alkylating metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]; this conversion is spontaneous, nonenzymatic, and occurs under physiologic conditions in all tissues to which it distributes. The cytotoxic effects of MTIC are manifested through alkylation (methylation) of DNA at the O^6, N^7 guanine positions which lead to DNA double strand breaks and apoptosis. Non-cell cycle specific.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and complete

Distribution: V_d: Parent drug: 0.4 L/kg; penetrates blood-brain barrier; CSF levels are ~35% to 39% of plasma levels (Yung 1999)

Protein binding: 15%

Metabolism: Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO_2 and 5-aminoimidazole-4-carboxamide (AIC), a natural constituent in urine; CYP isoenzymes play only a minor role in metabolism (of temozolomide and MTIC)

Bioavailability: Oral: 100% (on a mg-per-mg basis, IV temozolomide, infused over 90 minutes, is bioequivalent to an oral dose)

Half-life elimination: Mean: Parent drug: Children: 1.7 hours; Adults: 1.6-1.8 hours

Time to peak: Oral: Empty stomach: 1 hour; with food (high-fat meal): 2.25 hours

Excretion: Urine (~38%; parent drug 6%); feces <1%

Clearance: 5.5 L/hour/m^2; women have a ~5% lower clearance than men (adjusted for body surface area); children 3-17 years have similar temozolomide clearance as adults

Pricing: US

Capsules (Temodar Oral)

5 mg (5): $124.32

20 mg (5): $497.28

100 mg (5): $2486.40

140 mg (5): $3480.96

180 mg (5): $4475.52

250 mg (1): $1243.20

Capsules (Temozolomide Oral)

5 mg (5): $71.43

20 mg (5): $287.81

100 mg (5): $1438.80

140 mg (5): $2014.33

180 mg (5): $2589.84

250 mg (5): $3598.00

Solution (reconstituted) (Temodar Intravenous)

100 mg (1): $1095.29

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Advecit (TR); Astrodal (SG); Astromide (AU, NZ); Blastomat (HR, LV, NL, RO); Dralitem (EC, PY); Hliozomid (UA); Niman (CR, DO, GT, HN, NI, PA, SV); Rubrum ASF (CR, DO, GT, HN, NI, PA, SV); Temo (IL); Temobela (VN); Temodal (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IN, IQ,

IR, IT, JO, JP, KR, KW, LB, LT, LU, LY, MT, MX, MY, NI, NL, NO, NZ, OM, PA, PE, PH, PL, PR, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, SV, SY, TH, TR, TW, UA, UY, VE, VN, YE); Temodal IV (SG); Temolde (KR); Temomedac (IS); Temomedak (UA); Temonix (BD); Temotec (LK); Temovex (PH); Temozam (PH); Temozol (PH); Viztemo (UA); Zolomide (BD); Zolotem-250 (TH)

REFERENCES

1. *Agarwala SS, Kirkwood JM, Gore M, et al, " Temozolomide for the Treatment of Brain metastases Associated With Metastatic Melanoma: A Phase II Study," J Clin Oncol, 2004, 22(11):2101-7. [PubMed 15169796]*
2. *Alade SL, Brown RE, Paquet A. Polysorbate 80 and E-Ferol toxicity. Pediatrics. 1986;77(4):593-597. [PubMed 3960626]*
3. *Bagatell R, London WB, Wagner LM, et al, "Phase II Study of Irinotecan and Temozolomide in Children With Relapsed or Refractory Neuroblastoma: A Children's Oncology Group Study," J Clin Oncol, 2011, 29(2):208-13. [PubMed 21115869]*
4. *Brada M, Hoang-Xuan K, Rampling R, et al, "Multicenter Phase II Trial of Temozolomide in Patients With Glioblastoma Multiforme at First Relapse," Ann Oncol, 2001, 12(2):259-66. [PubMed 11300335]*
5. *Casey DA, Wexler LH, Merchant MS, et al, "Irinotecan and Temozolomide for Ewing Sarcoma: The Memorial Sloan-Kettering Experience," Pediatr Blood Cancer, 2009, 53(6):1029-34. [PubMed 19637327]*
6. *Centers for Disease Control (CDC). Unusual syndrome with fatalities among premature infants: association with a new intravenous vitamin E product. MMWR Morb Mortal Wkly Rep. 1984;33(14):198-199. http://www.cdc.gov/mmwr/preview/mmwrhtml/00000319.htm [PubMed 6423951]*
7. *Chan JA, Stuart K, Earle CC, et al, "Prospective Study of Bevacizumab Plus Temozolomide in Patients With Advanced Neuroendocrine Tumors," J Clin Oncol, 2012, 30(24):2963-8. [PubMed 22778320]*
8. *Di Giannatale A, Dias-Gastellier N, Devos A, et al. Phase II study of temozolomide in combination with topotecan (TOTEM) in relapsed or refractory neuroblastoma: a European Innovative Therapies for Children with Cancer-SIOP-European Neuroblastoma study. Eur J Cancer. 2014;50(1):170-177. [PubMed 24021349]*
9. *Dupuis LL, Boodhan S, Holdsworth M, et al; Pediatric Oncology Group of Ontario. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer. 2013;60(7):1073-1082. [PubMed 23512831]*
10. *Dupuis LL, Boodhan S, Sung L, et al; Pediatric Oncology Group of Ontario. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer. 2011;57(2):191-198. [PubMed 21465637]*
11. *Enting RH, Demopoulos A, DeAngelis LM, et al, "Salvage Therapy for Primary CNS Lymphoma With a Combination of Rituximab and Temozolomide," Neurology, 2004, 63(5):901-3. [PubMed 15365145]*
12. *Gan HK, Rosenthal MA, Dowling A, et al, "A Phase II Trial of Primary Temozolomide in Patients With Grade III Oligodendroglial Brain Tumors," Neuro Oncol, 2010, 12(5):500-7. [PubMed 20406900]*
13. *Garcia del Muro X, Lopez-Pousa A, Martin J, et al, "A Phase II Trial of Temozolomide as a 6-Week, Continuous, Oral Schedule in Patients With Advanced Soft Tissue Sarcoma: A Study by the Spanish Group for Research on Sarcomas," Cancer, 2005, 104(8):1706-12. [PubMed 16134177]*
14. *Griggs JJ, Mangu PB, Anderson H, et al, "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," J Clin Oncol, 2012, 30(13):1553-61. [PubMed 22473167]*
15. *Hegi ME, Diserens AC, Gorlia T, et al, "MGMT Gene Silencing and Benefit From Temozolomide in Glioblastoma," N Engl J Med, 2005, 352(10):997-1003. [PubMed 15758010]*
16. *Hegi ME, Liu L, Herman JG, et al, "Correlation of O6-Methylguanine Methyltransferase (MGMT) Promoter Methylation With Clinical Outcomes in Glioblastoma and Clinical Strategies to Modulate MGMT Activity," J Clin Oncol, 2008, 26(25):4189-99. [PubMed 18757334]*
17. *Isaksson M, Jansson L. Contact allergy to Tween 80 in an inhalation suspension. Contact Dermatitis. 2002;47(5):312-313. [PubMed 12534540]*

18. *Jalali R, Singh P, Menon H, et al, “Unexpected Case of Aplastic Anemia in a Patient With Glioblastoma Multiforme Treated With Temozolomide,” J Neurooncol, 2007, 85(1):105-7. [PubMed 17505778]*
19. *Kesari S, Schiff D, Drappatz J, et al, “Phase II Study of Protracted Daily Temozolomide for Low-Grade Gliomas in Adults,” Clin Cancer Res, 2009, 15(1):330-7. [PubMed 19118062]*
20. *Kulke MH, Stuart K, Enzinger PC, et al, “Phase II Study of Temozolomide and Thalidomide in Patients With Metastatic Neuroendocrine Tumors,” J Clin Oncol, 2006, 24(3):401-6. [PubMed 16421420]*
21. *Lucente P, Iorizzo M, Pazzaglia M. Contact sensitivity to Tween 80 in a child. Contact Dermatitis. 2000;43(3):172. [PubMed 10985636]*
22. *Marchesi F, Turriziani M, Tortorelli G, et al, “Triazene Compounds: Mechanism of Action and Related DNA Repair Systems,” Pharmacol Res, 2007, 56(4):275-87. [PubMed 17897837]*
23. *Middleton MR, Grob JJ, Aaronson N, et al, “Randomized Phase III Study of Temozolomide Versus Dacarbazine in the Treatment of Patients With Advanced Metastatic Malignant Melanoma,” J Clin Oncol, 2000, 18(1):158-66. [PubMed 10623706]*
24. *Mikkelsen T, Doyle T, Anderson J, et al, “Temozolomide Single-Agent Chemotherapy for Newly Diagnosed Anaplastic Oligodendroglioma,” J Neurooncol, 2009, 92(1):57-63. [PubMed 19011763]*
25. *Park MS, Patel SR, Ludwig JA, et al, “Activity of Temozolomide and Bevacizumab in the Treatment of Locally Advanced, Recurrent, and Metastatic Hemangiopericytoma and Malignant Solitary Fibrous Tumor,” Cancer, 2011, 117(21):4939-47. [PubMed 21480200]*
26. *Perry JR, Bélanger K, Mason WP, et al, "Phase II Trial of Continuous Dose-Intense Temozolomide in Recurrent Malignant Glioma: RESCUE Study," J Clin Oncol, 2010, 28(12):2051-7. [PubMed 20308655]*
27. *Querfeld C, Rosen ST, Guitart J, et al, “Multicenter Phase II Trial of Temozolomide in Mycosis Fungoides/Sezary Syndrome: Correlation With O^6-Methylguanine-DNA Methyltransferase and Mismatch Repair Proteins,” Clin Cancer Res, 2011, 17(17):5748-54. [PubMed 21747120]*
28. *Roila F, Herrstedt J, Aapro M, et al, "Guideline Update for MASCC and ESMO in the Prevention of Chemotherapy- and Radiotherapy-Induced Nausea and Vomiting: Results of the Perugia Consensus Conference," Ann Oncol, 2010, 21(Suppl 5):v232-43. [PubMed 20555089]*
29. *Sarganas G, Orzechowski HD, Klimpel A, et al. Severe sustained cholestatic hepatitis following temozolomide in a patient with glioblastoma multiforme: case study and review of data from the FDA adverse event reporting system. Neuro Oncol. 2012;14(5):541-546. doi: 10.1093/neuonc/nos056. [PubMed 22394496]*
30. *Shelley WB, Talanin N, Shelley ED. Polysorbate 80 hypersensitivity. Lancet. 1995;345(8980):1312-1313. [PubMed 7746084]*
31. *Strosberg JR, Fine RL, Choi J, et al, “First-line Chemotherapy With Capecitabine and Temozolomide in Patients With Metastatic Pancreatic Endocrine Carcinomas,” Cancer, 2011, 117(2):268-75. [PubMed 20824724]*
32. *Stupp R, Dietrich PY, Ostermann Kraljevic S, et al, “Promising Survival for Patients With Newly Diagnosed Glioblastoma Multiforme Treated With Concomitant Radiation Plus Temozolomide Followed by Adjuvant Temozolomide,” J Clin Oncol, 2002, 20(5):1375-82. [PubMed 11870182]*
33. *Stupp R, Gander M, Leyvraz S, et al, “Current and Future Developments in the Use of Temozolomide for the Treatment of Brain Tumours,” Lancet Oncol, 2001, 2(9):552-60. [PubMed 11905710]*
34. *Stupp R, Hegi ME, Mason WP, et al, “Effects of Radiotherapy With Concomitant and Adjuvant Temozolomide Versus Radiotherapy Alone on Survival in Glioblastoma in a Randomised Phase III Study: 5-year Analysis of the EORTC-NCIC Trial,” Lancet Oncol, 2009, 10(5):459-66. [PubMed 19269895]*
35. *Stupp R, Mason WP, van den Bent MJ, et al, “Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma,” N Engl J Med, 2005, 352(10):987-96. [PubMed 15758009]*
36. *Tani M, Fina M, Alinari L, et al, “Phase II Trial of Temozolomide in Patients With Pretreated Cutaneous T-Cell Lymphoma,” Haematologica, 2005, 90(9):1283-4. [PubMed 16154858]*
37. *Tawbi HA, Beumer JH, Tarhini AA, et al. Safety and efficacy of decitabine in combination with temozolomide in metastatic melanoma: a phase I/II study and pharmacokinetic analysis. Ann Oncol. 2013;24(4):1112-1119. doi: 10.1093/annonc/mds591 [PubMed 23172636]*
38. *Temodal (temozolomide) [product monograph]. Kirkland, Quebec, Canada: Merck Canada Inc; May 2016.*

39. *Temodar (temozolomide) [prescribing information]. Whitehouse Station, NJ: Merck & Co, Inc; September 2015.*

40. *Trissel LA, Zhang Y, Koontz SE. Temozolomide Stability in Extemporaneously Compounded Oral Suspensions. Int J Pharm Compd. 2006;10(5):396-399. [PubMed 23974320]*

41. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf. Updated September 2016. Accessed October 5, 2016.*

42. *Villano JL, Collins CA, Manasanch EE, et al, "Aplastic Anaemia in Patient With Glioblastoma Multiforme Treated With Temozolomide," Lancet Oncol, 2006, 7(5):436-8. [PubMed 16648049]*

43. *Villano JL, Letarte N, Yu JM, et al, "Hematologic Adverse Events Associated With Temozolomide," Cancer Chemother Pharmacol, 2012, 69(1):107-13. [PubMed 21614470]*

44. *Villano JL, Seery TE and Bressler LR, "Temozolomide in Malignant Gliomas: Current Use and Future Targets," Cancer Chemother Pharmacol, 2009, 64(4):647-55. [PubMed 19543728]*

45. *Wong ET, Tishler R, Barron L, et al, "Immunochemotherapy With Rituximab and Temozolomide for Central Nervous System Lymphomas," Cancer, 2004, 101(1):139-45. [PubMed 15221999]*

46. *Yung WK, Albright RE, Olson J, et al, "A Phase II Study of Temozolomide vs Procarbazine in Patients With Glioblastoma Multiforme at First Relapse," Br J Cancer, 2000, 83(5):588-93. [PubMed 10944597]*

47. *Yung WK, Prados MD, Yaya-Tur R, et al, "Multicenter Phase II Trial of Temozolomide in Patients With Anaplastic Astrocytoma or Anaplastic Oligoastrocytoma at First Relapse," J Clin Oncol, 1999, 17(9):2762-71. [PubMed 10561351]*

Topic 9699 Version 163.0