Temozolomide:

Class:

- Antineoplastic Agent, Alkylating Agent (Triazene)

Indications:

- **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)
- *Canadian labeling:* Treatment of newly-diagnosed glioblastoma multiforme (initially in combination with radiotherapy, then as maintenance treatment), treatment of recurrent or progressive glioblastoma multiforme or anaplastic astrocytoma

Unlabeled use :

- Treatment of recurrent glioblastoma multiforme,
- low-grade astrocytoma,
- low-grade oligodendroglioma,
- anaplastic oligodendroglioma,
- metastatic CNS lesions,
- refractory primary CNS lymphoma,
- advanced or metastatic melanoma,
- advanced cutaneous T-cell lymphomas (mycosis fungoides [MF] and Sézary syndrome [SS]),
- advanced neuroendocrine tumors (carcinoid or islet cell),
- Ewing's sarcoma (recurrent or progressive),
- soft tissue sarcomas (extremity/retroperitoneal/intra-abdominal or hemangiopericytoma/solitary fibrous tumor),
- treatment of pediatric neuroblastoma

Available dosage form in the hospital:

- 20 mg capsule
- 100 mg capsule

Trade Names:

Astromide , Dralitem , Temo , Temodal ,Temodal IV , Temozam , Temozol , **Temodar**

Dosage:

Note: Temozolomide is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting. Prior to dosing, ANC should be ≥1500/mm^3 and platelets ≥100,000/mm^3.

-Anaplastic astrocytoma (refractory): Oral, I.V.: Initial dose: 150 mg/m^2 once daily for 5 consecutive days of a 28-day treatment cycle. If ANC ≥1500/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 <1000/mm^3 or platelets <50,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1500/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 1000-1500/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 >1500/mm^3 and platelets >100,000/mm^3; maintain initial dose

-Glioblastoma multiforme (newly diagnosed, high-grade glioma): Oral, I.V.:

-Concomitant phase: 75 mg/m^2/day 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/day throughout the 42-day concomitant phase (up to 49 days) as long as ANC ≥1500/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 <1500/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 within 48 hours of day 22; hold next cycle and do weekly CBC until ANC >1500/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 2-6: May increase to 200 mg/m^2 once daily for 5 days; repeat every 28 days (if ANC ≥1500/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 3-6)

***Dosage modification (during maintenance phase) for toxicity:*

-ANC <1000/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

-**Glioblastoma multiforme (recurrent glioma):** *Canadian labeling (unlabeled use in the U.S.):* 200 mg/m^2/day for 5 days every 28 days; if previously treated with chemotherapy, initiate at 150 mg/m^2/day for 5 days every 28 days and increase to 200 mg/m^2/day for 5 days every 28 days with cycle 2 if no hematologic toxicity (Brada, 2001; Yung, 2000)

-**Cutaneous T-cell lymphoma, advanced (mycosis fungoides [MF] and Sézary syndrome [SS]; unlabeled 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 (unlabeled use):** Oral: 100 mg/m^2/dose days 1-5 every 21 days (in combination with irinotecan) (Casey, 2009)

-**Melanoma, advanced or metastatic (unlabeled use):** Oral: 200 mg/m^2/day 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 (unlabeled use):** Oral: 150 mg/m^2/day 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 (unlabeled use):** Oral: 150 mg/m^2/day for 5 days every 28 days, initially in combination with rituximab, followed by temozolomide monotherapy: 150 mg/m^2/day for 5 days every 28 days (Wong, 2004) **or** 150 mg/m^2/day for 7 days every 14 days, initially in combination with rituximab, followed by temozolomide monotherapy: 150 mg/m^2/day for 5 days every 28 days (Enting, 2004)

-**Soft tissue sarcoma (unlabeled use):** Oral:

- *Soft tissue sarcoma, metastatic or unresectable:* 75 mg/m^2/day 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)

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.

Renal Impairment:

Oral:

Cl_{cr} ≥36 mL/minute/m^2: No dosage adjustment provided in the manufacturer's labeling, however, dosage adjustment is not likely needed as no effect on temozolomide clearance was demonstrated.

Severe renal impairment (Cl_{cr} <36 mL/minute/m^2): No dosage adjustment provided in manufacturer's labeling; use with caution (has not been studied).

Dialysis patients: No dosage adjustment provided in manufacturer's labeling (has not been studied).

Hepatic Impairment:

-Mild-to-moderate impairment: No dosage adjustment provided in manufacturer's labeling; however, pharmacokinetics are similar to patients with normal hepatic function.

-Severe hepatic impairment: No dosage adjustment provided in 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).

Common side effect:

- Cardiovascular: Peripheral edema (11%)
- Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)
- Dermatologic: Alopecia (55%), 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: Lymphopenia (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%)
- Neuromuscular & skeletal: Weakness (7% to 13%)
- Miscellaneous: Viral infection (11%)

Pregnancy Risk Factor: D