

**DRUG NAME: Temozolomide****SYNONYM(S):** TMZ, SCHS2.365, NSC 362856**COMMON TRADE NAME(S):** TEMODAL®, TEMODAR®**CLASSIFICATION:** Alkylating agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Temozolomide undergoes rapid chemical conversion at physiologic pH to the active compound, monomethyl triazeno imidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to methylation of DNA at the O<sup>6</sup> position of guanine.<sup>1,2</sup> Both temozolomide and dacarbazine are prodrugs of MTIC. Unlike dacarbazine, temozolomide does not require metabolic activation by the cytochrome P450. The antitumour activity of temozolomide is schedule dependent. By compressing the schedule, it may be possible to give subsequent doses of temozolomide when levels of the DNA repair protein O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) are low, thereby prolonging systemic exposure to the drug and MTIC to improve cytotoxicity and response rate. A 12-hour regimen has been tested, and clinical trials involving 4- and 8-hour schedules are under way.<sup>3</sup>

**PHARMACOKINETICS:**

Interpatient variability	minimal inpatient and interpatient variability <sup>4</sup>	
Oral Absorption	rapidly and completely absorbed, with 100% bioavailability. <sup>5</sup> Food delays absorption but is clinically insignificant. <sup>1</sup> Consistency of administration with respect to food is recommended. <sup>6</sup>	
	time to peak plasma concentration	1 h <sup>4</sup> ; increased to 2.3 h after high fat meal <sup>4</sup>
Distribution	extensive tissue distribution <sup>3</sup> ; equilibrium between plasma and ascitic fluid reached after 2 h <sup>7</sup>	
	cross blood brain barrier?	9-29% of serum concentration <sup>7</sup>
	volume of distribution	15-18 L/m <sup>2</sup> (oral) <sup>8,9</sup> ; 0.4 ± 0.1 L/kg (intravenous) <sup>7</sup>
	plasma protein binding	10-20%
Metabolism	rapid, spontaneous, pH-dependent formation of MTIC <sup>8</sup>	
	active metabolite(s)	MTIC
	inactive metabolite(s)	amino imidazole carboxamide (AIC), temozolomide acid metabolite (TMA)
Excretion	major pathways are non-enzymatic hydrolysis (to MTIC) and renal excretion of parent drug <sup>10</sup>	
	urine	38% recovered over 7 days (6% unchanged, 12% as AIC, 2% as TMA, and 17% as unidentified polar metabolites) <sup>4,9</sup>
	feces <sup>11,12</sup>	<1%
	terminal half life	temozolomide: 1.8 h (oral) <sup>1</sup> ; 92 ± 14 min (intravenous) <sup>7</sup> MTIC: 1.5-1.8 h <sup>1,13</sup>
	clearance	115 mL/min/m <sup>2</sup> (87-155 mL/min/m <sup>2</sup> ) (oral) <sup>8</sup> ; 220 ± 48 mL/min (intravenous) <sup>7</sup>
Gender	women have 5% lower clearance and higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy. <sup>6</sup>	

Elderly	clearance independent of age; patients older than 70 years have a higher incidence of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy. <sup>6</sup>
Children	Children over 3 years have 15-30% higher serum levels <sup>14</sup> and 40% higher AUC, probably due to higher body surface area to weight ratio. <sup>1</sup> However, maximum tolerated dose is 1000 mg/m <sup>2</sup> /cycle in both children and adults. Time to peak concentration and half-life similar to those in adults.

Adapted from reference<sup>1</sup> unless specified otherwise.

## USES:

### **Primary uses:**

- \* Astrocytoma<sup>15</sup>
- \* Glioblastoma<sup>18,19</sup>

### **Other uses:**

- Brain metastases from solid tumours<sup>16,17</sup>
- Melanoma<sup>3</sup>

\* Health Canada Therapeutic Products Programme approved indication

## SPECIAL PRECAUTIONS:

### **Contraindications:**

- history of hypersensitivity reaction to temozolomide or dacarbazine<sup>1</sup>

### **Caution:**

- **hepatic injury**, including fatal hepatic failure, has been reported; baseline liver function tests prior to treatment and ongoing periodic monitoring are recommended<sup>20,21</sup>

**Carcinogenicity:** Carcinogenic in rats.<sup>6</sup>

**Mutagenicity:** Mutagenic in Ames test and clastogenic in mammalian *in vitro* mutation tests.<sup>6</sup>

**Fertility:** Temozolomide has been linked to testicular toxicity in animal studies, and may have additional reproductive effects, including infertility and genotoxicity. As infertility may be irreversible, men are advised to seek advice on cryoconservation of sperm prior to treatment.<sup>22</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>6</sup> There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Men and women are advised to use an effective method of birth control during and for 6 months after treatment.<sup>22</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>1</sup>

## SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

<b>ORGAN SITE</b>	<b>SIDE EFFECT</b>
Dose-limiting side effects are in <b>bold, italics</b>	
blood/bone marrow	anemia (2%, severe 1%)
febrile/neutropenia	leukopenia (4%, severe 4%)

<b>ORGAN SITE</b>	<b>SIDE EFFECT</b>
Dose-limiting side effects are in <b>bold, italics</b>	
	<b>neutropenia</b> (4%, severe 4%); nadir 21-28 days, recovery within 14 days of nadir pancytopenia (<1%, severe 0.5%) <b>thrombocytopenia</b> (9%, severe 9%); nadir 21-28 days, recovery within 14 days of nadir
cardiovascular (general)	edema <sup>6,19</sup> (1%, severe 1%) embolism, pulmonary (severe 0.3%) thrombophlebitis (severe 0.5%)
constitutional symptoms	asthenia (5%, severe 2%) fatigue (23%, severe 2%) fever (4%, severe 0.5%) malaise (2%) weight loss (1%)
dermatology/skin	<b>extravasation hazard: irritant</b> <sup>22-24</sup> alopecia (4%) injection site reactions, <sup>22</sup> including erythema, irritation, pain, pruritus, swelling, warmth (<1%) <sup>23</sup> ; usually mild and short-lived <sup>22</sup> pruritus (3%) rash (5%)
endocrine	hot flashes (rare) <sup>25</sup> ovarian suppression (rare) <sup>25</sup>
gastrointestinal	<b>emetogenic potential: high moderate</b> <sup>4</sup> anorexia (9%) constipation (15%, severe 0.5%) dehydration (severe 0.5%) diarrhea (7%, severe 0.5%) dyspepsia (2%) nausea (41%, severe 5%) taste disturbance (1%) vomiting (34%, severe 4%)
hemorrhage	CNS hemorrhage (severe 0.3%) hemorrhage (severe 0.5%) petechiae/purpura (4%, severe 0.3%)
hepatobiliary (see paragraph following <b>Side Effects</b> table)	cholestasis <sup>20</sup> <b>hepatic failure</b> <sup>20</sup> ; sometimes fatal hepatitis <sup>20</sup>
infection	pulmonary infection (severe 0.5%)
investigations	AST/ALT elevation <sup>20</sup> (1-5%) gamma-glutamyltransferase elevation <sup>20</sup> (1%) hyperbilirubinemia <sup>20</sup> liver enzyme elevation <sup>20</sup> (1%)
metabolic/laboratory	hyperglycemia (severe 0.5%)
neurology	amnesia <sup>6</sup>

<b>ORGAN SITE</b>	<b>SIDE EFFECT</b>
Dose-limiting side effects are in <b><i>bold, italics</i></b>	
	confusion (severe 0.5%)
	consciousness decreased (severe 0.3%)
	CNS cerebrovascular ischemia (severe 0.3%)
	depression (1%)
	dizziness (2%)
	insomnia (2%)
	neuropathy, motor (severe 1%)
	neuropathy, sensory (2%)
	seizures (3%, severe 0.5%)
	somnolence (4%, severe 0.8%)
pain	abdominal pain (3%, severe 0.5%)
	headache (11%, severe 2%)
	myalgia (1%)
	pain (3%)
pulmonary	pneumonia (severe 0.5%)
	dyspnea (2%)

Adapted from reference<sup>1</sup> unless specified otherwise.

**Hematologic toxicities:** The incidence of thrombocytopenia and neutropenia was approximately three times higher in females. Pediatric patients appeared to tolerate higher plasma concentrations of temozolomide before reaching dose limiting toxicity. This is likely due to increased bone marrow reserves in pediatric patients.<sup>1</sup>

**Hepatotoxicity,** including liver enzyme elevation, hyperbilirubinemia, cholestasis, hepatitis, and fatal hepatic failure, has been observed with temozolomide and may occur several weeks or more after the last treatment. Liver function should be assessed prior to treatment initiation and then regularly throughout treatment.<sup>20,21</sup> Refer to protocol by which patient is being treated.

**Nausea and vomiting** may be reduced by taking temozolomide on an empty stomach.<sup>1</sup>

#### INTERACTIONS:

<b>AGENT</b>	<b>EFFECT</b>	<b>MECHANISM</b>	<b>MANAGEMENT</b>
carbamazepine	no effect on temozolomide clearance		
dexamethasone	no effect on temozolomide clearance		
H2-antagonists (eg, ranitidine)	no effect on clearance <sup>1</sup> or oral absorption of temozolomide <sup>26</sup>		
ondansetron	no effect on temozolomide clearance		
phenobarbital	no effect on temozolomide clearance		
phenytoin	no effect on temozolomide clearance		
prochlorperazine	no effect on temozolomide clearance		
tobacco	no effect on temozolomide clearance		

<b>AGENT</b>	<b>EFFECT</b>	<b>MECHANISM</b>	<b>MANAGEMENT</b>
valproic acid	possible increase of temozolomide toxicity	5% decrease (not clinically significant) in temozolomide clearance	no clinical interventions appear necessary

Adapted from reference<sup>1</sup> unless specified otherwise.

**Cytochrome P450 (CYP450)-mediated metabolism** did not contribute significantly to the plasma clearance of temozolomide. Consequently, clearance of temozolomide should not be affected to a clinically meaningful degree by interaction of concurrent medications with specific isozymes of CYP450 nor would administration of temozolomide alter, by competitive inhibition, the metabolism of other drugs. Analysis of data from Phase II studies confirmed that clearance of temozolomide was unaffected by 7 medications (ie, see table above) commonly used by this patient population.<sup>1</sup>

### SUPPLY AND STORAGE:

**Oral:** Merck Canada Inc. supplies temozolomide as 5 mg, 20 mg, 100 mg, 140 mg, and 250 mg capsules; inactive ingredients include lactose. Store at room temperature. Protect from moisture.<sup>27</sup>

### SOLUTION PREPARATION AND COMPATIBILITY:

**Additional information:** Temozolomide capsules have been used for the extemporaneous compounding of an oral suspension<sup>28</sup>

### PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion <sup>22</sup>	over 90 minutes
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

### DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or in patients with other toxicities.

**Adults:**BC Cancer usual dose noted in ***bold, italics***

Oral:	Cycle length:	
	<b>4 weeks</b> <sup>1,22,23,29-31</sup> :	<b><i>150 mg/m<sup>2</sup></i></b> (range 100-200 mg/m <sup>2</sup> ) <b><i>PO once daily for 5 consecutive days starting on day 1</i></b> <b><i>or</i></b> <b><i>for 5 consecutive days starting on day 10</i></b> (total dose per cycle = 750 mg/m <sup>2</sup> [range 500-1000 mg/m <sup>2</sup> ]) Round dose to the nearest 5 mg.
	<b>4 weeks</b> <sup>32-34</sup> :	<b><i>50-100 mg/m<sup>2</sup> PO once daily for 21-28 consecutive days starting on day 1</i></b> Round dose to the nearest 5 mg.
		Administer with food or on an empty stomach, as long as timing in relation to meals is consistent. Administration on an empty stomach or at bedtime may help reduce nausea and vomiting. <sup>23</sup>
Injection <sup>22</sup> :	4 weeks:	150 mg/m <sup>2</sup> (range 100-200 mg/m <sup>2</sup> ) IV once daily for 5 consecutive days starting on day 1 (total dose per cycle = 750 mg/m <sup>2</sup> [range 500-1000 mg/m <sup>2</sup> ])
Concurrent radiation <sup>10,35-38</sup> :	3-7 weeks:	<b><i>75 mg/m<sup>2</sup> PO once daily starting on day 1</i></b> Round dose to the nearest 5 mg.
Dosage in myelosuppression:		modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure <sup>23</sup> :		use with caution if creatinine clearance <36 mL/min
Dosage in hepatic failure:		no information found
Dosage in dialysis:		no information found

**Children:**

Oral <sup>1</sup> :	Cycle length:	
	4 weeks:	150 mg/m <sup>2</sup> (range 100-200 mg/m <sup>2</sup> ) PO once daily for 5 consecutive days starting on day 1 (total dose per cycle 750 mg/m <sup>2</sup> [range 500-1000 mg/m <sup>2</sup> ]) Round dose to the nearest 5 mg.
		Administer with food or on an empty stomach, as long as timing in relation to meals is consistent. Administration on an empty stomach or at bedtime may help reduce nausea and vomiting. <sup>23</sup>
Injection <sup>22</sup> :	4 weeks:	150 mg/m <sup>2</sup> (range 100-200 mg/m <sup>2</sup> ) IV once daily for 5 consecutive days starting on day 1 (total dose per cycle = 750 mg/m <sup>2</sup> [range 500-1000 mg/m <sup>2</sup> ])

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