

TEMOZOLOMIDE- temozolomide capsule AvPAK

HIGHLIGHTS OF PRESCRIBING INFORMATION Temozolomide Capsules

These highlights do not include all the information needed to use TEMOZOLOMIDE CAPSULES safely and effectively. See full prescribing information for TEMOZOLOMIDE CAPSULES.

TEMOZOLOMIDE capsules for oral use

Initial U.S. Approval: 1999

INDICATIONS AND USAGE

Temozolomide capsules are an alkylating drug indicated for the treatment of adult patients with:

- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment. (1.1)
- Refractory anaplastic astrocytoma patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. (1.2)

DOSAGE AND ADMINISTRATION

- Newly Diagnosed GBM: 75 mg/m² for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m² once daily for Days 1 to 5 of a 28-day cycle of temozolomide capsules for 6 cycles. (2.1)
- Refractory Anaplastic Astrocytoma: Initial dose 150 mg/m² once daily for 5 consecutive days per 28-day treatment cycle. (2.1)

DOSAGE FORMS AND STRENGTHS

- 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules. (3)

CONTRAINDICATIONS

- Known hypersensitivity to any temozolomide component or to dacarbazine (DTIC). (4.1)

WARNINGS AND PRECAUTIONS

- Myelosuppression - monitor Absolute Neutrophil Count (ANC) and platelet count prior to dosing and throughout treatment. Geriatric patients and women have a higher risk of developing myelosuppression. (5.1)
- Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed. (5.2)
- *Pneumocystis* pneumonia (PCP) - PCP prophylaxis required for all patients receiving concomitant temozolomide and radiotherapy for the 42-day regimen for the treatment of newly diagnosed glioblastoma multiforme. (5.3)
- All patients, particularly those receiving steroids, should be observed closely for the development of lymphopenia and PCP. (5.4)
- Complete blood counts should be obtained throughout the treatment course as specified. (5.4)
- Hepatotoxicity - fatal and severe hepatotoxicity have been reported. Perform liver function tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of temozolomide. (5.5)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving temozolomide. (5.6)

ADVERSE REACTIONS

- The most common adverse reactions (≥10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia. (6.1)
- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) that have

developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia. (6.1)

- Allergic reactions have also been reported. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE, Inc. at 1-855-361-3993 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- DRUG INTERACTIONS -----

- Valproic acid: decreases oral clearance of temozolomide. (7.1)

----- USE IN SPECIFIC POPULATIONS -----

- Nursing mothers: Not recommended. (8.3)
- Pediatric use: No established use. (8.4)
- Hepatic/Renal Impairment: Caution should be exercised when temozolomide is administered to patients with severe renal or hepatic impairment. (8.6,8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Glioblastoma Multiforme

Temozolomide capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

1.2 Refractory Anaplastic Astrocytoma

Temozolomide capsules are 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing and Dose Modification Guidelines

Dosage of temozolomide capsules 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. For temozolomide capsules dosage calculations based on body surface area (BSA) see **Table 5**. For suggested capsule combinations on a daily dose see **Table 6**.

Patients with Newly Diagnosed High Grade Glioma: Concomitant Phase:

Temozolomide capsules are administered at 75 mg/m² daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance temozolomide capsules for 6 cycles. Focal RT includes the tumor bed or resection site with a 2- to 3-cm margin. No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The temozolomide capsules 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) nonhematological toxicity \leq Grade 1 (except for alopecia, nausea, and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and nonhematological toxicity criteria as noted in **Table 1**. *Pneumocystis pneumonia* (PCP) prophylaxis is required during the concomitant administration of temozolomide capsules and radiotherapy, and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC Grade ≤ 1).

TABLE 1: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	≥ 0.5 and $< 1.5 \times 10^9$ /L	$< 0.5 \times 10^9$ /L
Platelet Count	≥ 10 and $< 100 \times 10^9$ /L	$< 10 \times 10^9$ /L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

*Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count $\geq 1.5 \times 10^9$ /L; platelet count $\geq 100 \times 10^9$ /L; CTC nonhematological toxicity \leq Grade 1 (except for alopecia, nausea, vomiting). TMZ=temozolomide; CTC=Common Toxicity Criteria.

Maintenance Phase:

Cycle 1: Four weeks after completing the temozolomide capsules+RT phase, temozolomide capsules are administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m² once daily for 5 days followed by 23 days without treatment.

Cycles 2 to 6: At the start of Cycle 2, the dose can be escalated to 200 mg/m², if the CTC nonhematologic toxicity for Cycle 1 is Grade ≤ 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/m² per day for the first 5 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.

Dose Reduction or Discontinuation During Maintenance: Dose reductions during the maintenance phase should be applied according to **Tables 2** and **3**.

During treatment, a complete blood count should be obtained on Day 22 (21 days after

the first dose of temozolomide capsules) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ ($1500/\mu L$) and the platelet count exceeds $100 \times 10^9/L$ ($100,000/\mu L$). The next cycle of temozolomide capsules 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 nonhematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to **Tables 2** and **3**.

TABLE 2: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m ² /day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2 to 6 in absence of toxicity

TABLE 3: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	$<1.0 \times 10^9/L$	See footnote †
Platelet Count	$<50 \times 10^9/L$	See footnote †
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4 †

*TMZ dose levels are listed in **Table 2**.

†TMZ is to be discontinued if dose reduction to $<100 \text{ mg/m}^2$ is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. TMZ=temozolomide; CTC=Common Toxicity Criteria.

Patients with Refractory Anaplastic Astrocytoma: For adults the initial dose is 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are $\geq 1.5 \times 10^9/L$ ($1500/\mu L$) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9/L$ ($100,000/\mu L$), the temozolomide capsules dose may be increased to $200 \text{ mg/m}^2/\text{day}$ for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/L$ ($1500/\mu L$) and the platelet count exceeds $100 \times 10^9/L$ ($100,000/\mu L$). The next cycle of temozolomide capsules should not be started until the ANC and platelet count exceed these levels. If the ANC falls to $<1.0 \times 10^9/L$ ($1000/\mu L$) or the platelet count is $<50 \times 10^9/L$ ($50,000/\mu L$) during any cycle, the next cycle should be reduced by 50 mg/m^2 , but not below 100 mg/m^2 , the lowest recommended dose (see **Table 4**). Temozolomide capsules therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of

therapy is not known.

TABLE 4: Dosing Modification Table

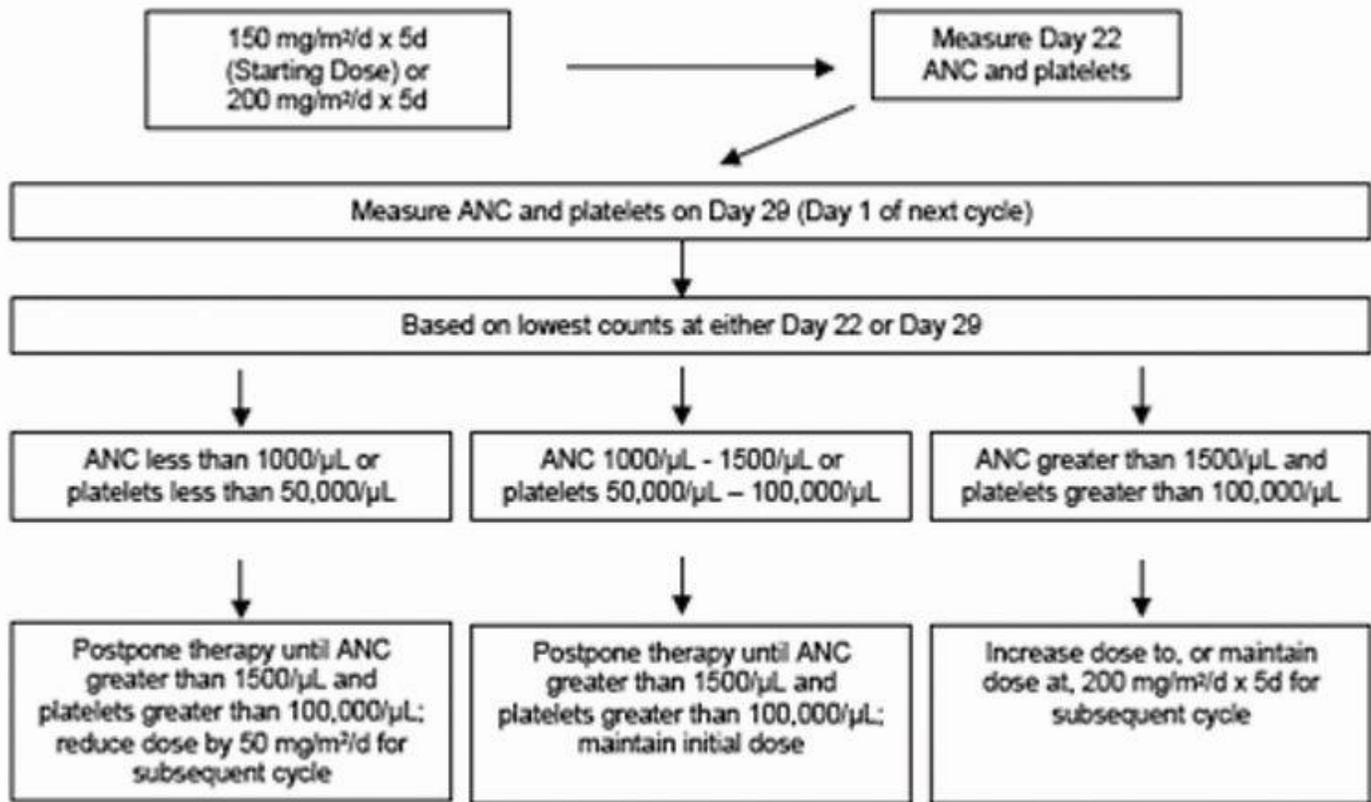


TABLE 5: Daily Dose Calculations by Body Surface Area (BSA)

Total BSA (m ²)	75 mg/m ² (mg daily)	150 mg/m ² (mg daily)	200 mg/m ² (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

TABLE 6: Suggested Capsule Combinations Based on Daily Dose in Adults

Number of Daily Capsules by Strength (mg)						
Total Daily Dose (mg)	250 mg	180 mg	140 mg	100 mg	20 mg	5 mg
75	0	0	0	0	3	3
82.5	0	0	0	0	4	0
90	0	0	0	0	4	2
97.5	0	0	0	1	0	0
105	0	0	0	1	0	1
112.5	0	0	0	1	0	2
120	0	0	0	1	1	0
127.5	0	0	0	1	1	1
135	0	0	0	1	1	3
142.5	0	0	1	0	0	0
150	0	0	1	0	0	2
157.5	0	0	1	0	1	0
165	0	0	1	0	1	1
172.5	0	0	1	0	1	2
180	0	1	0	0	0	0
187.5	0	1	0	0	0	1
195	0	1	0	0	0	3
200	0	1	0	0	1	0
210	0	0	0	2	0	2
220	0	0	0	2	1	0
225	0	0	0	2	1	1
240	0	0	1	1	0	0
255	1	0	0	0	0	1
260	1	0	0	0	0	2
270	1	0	0	0	1	0
280	0	0	2	0	0	0
285	0	0	2	0	0	1
300	0	0	0	3	0	0
315	0	0	0	3	0	3
320	0	1	1	0	0	0
330	0	1	1	0	0	2
340	0	1	1	0	1	0
345	0	1	1	0	1	1
360	0	2	0	0	0	0
375	0	2	0	0	0	3
380	0	1	0	2	0	0
400	0	0	0	4	0	0
420	0	0	3	0	0	0
440	0	0	3	0	1	0
460	0	2	0	1	0	0
480	0	1	0	3	0	0

2.2 Preparation and Administration

Temozolomide Capsules: In clinical trials, temozolomide capsules were administered under both fasting and nonfasting conditions; however, absorption is affected by food [see *Clinical Pharmacology (12.3)*], and consistency of administration with respect to food is recommended. There are no dietary restrictions with temozolomide capsules. To reduce nausea and vomiting, temozolomide capsules should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of temozolomide capsules.

Temozolomide capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

If capsules are accidentally opened or damaged, precautions should be taken to avoid inhalation or contact with the skin or mucous membranes [see *How Supplied/Storage and Handling (16.1)*].

3 DOSAGE FORMS AND STRENGTHS

- Temozolomide capsules for oral administration
 - **5 mg** capsules have green opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "801" with black ink.
 - **20 mg** capsules have yellow opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "802" with black ink.
 - **100 mg** capsules have pink opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "803" with black ink.
 - **140 mg** capsules have blue opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "804" with black ink.
 - **180 mg** capsules have red opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "805" with black ink.
 - **250 mg** capsules have white opaque color caps imprinted "AMNEAL" and white opaque color bodies imprinted "806" with black ink.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Temozolomide is contraindicated in patients who have a history of hypersensitivity reaction (such as urticaria, allergic reaction including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome) to any of its components. Temozolomide is also contraindicated in patients who have a history of hypersensitivity to dacarbazine (DTIC), since both drugs are metabolized to 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC).

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with temozolomide may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medications associated with aplastic anemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, patients must have an absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$ and a platelet count $\geq 100 \times 10^9/\text{L}$. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above $1.5 \times 10^9/\text{L}$ and platelet count exceeds $100 \times 10^9/\text{L}$. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

5.2 Myelodysplastic Syndrome

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed.

5.3 Pneumocystis Pneumonia

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against *Pneumocystis* 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. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP regardless of the regimen.

5.4 Laboratory Tests

For the concomitant treatment phase with RT, a complete blood count should be obtained prior to initiation of treatment and weekly during treatment.

For the 28-day treatment cycles, a complete blood count should be obtained prior to treatment on Day 1 and on Day 22 (21 days after the first dose) of each cycle. Blood counts should be performed weekly until recovery if the ANC falls below $1.5 \times 10^9/\text{L}$ and the platelet count falls below $100 \times 10^9/\text{L}$ [see *Recommended Dosing and Dose Modification Guidelines (2.1)*].

5.5 Hepatotoxicity

Fatal and severe hepatotoxicity have been reported in patients receiving temozolomide. Perform liver function tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately two to four weeks after the last dose of temozolomide.

5.6 Use in Pregnancy

Temozolomide can cause fetal harm when administered to a pregnant woman. Administration of temozolomide to rats and rabbits during organogenesis at 0.38 and 0.75 times the maximum recommended human dose (75 and $150 \text{ mg}/\text{m}^2$), respectively, caused numerous fetal malformations of the external organs, soft tissues, and skeleton in both species [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Glioblastoma Multiforme: During the concomitant phase (temozolomide+radiotherapy), adverse reactions including thrombocytopenia, nausea, vomiting, anorexia, and constipation were more frequent in the temozolomide+RT arm. The incidence of other adverse reactions was comparable in the two arms. The most common adverse reactions across the cumulative temozolomide experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (see **Table 7**). Forty-nine percent (49%) of patients treated with temozolomide reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Overall, the pattern of reactions during the maintenance phase was consistent with the known safety profile of temozolomide.

Adverse Reactions (≥ 5%) in Patients Receiving Temozolomide in Newly Diagnosed Glioblastoma Trial

Adverse Reactions	Concomitant Phase				Maintenance Phase	
	Radiation Therapy and Temozolomide N = 288*		Radiation Therapy Alone N = 285		Temozolomide N=224	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grades ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Skin and Subcutaneous Tissue						
Alopecia	69		63		55	
Rash	19	1	15		13	1
Dry Skin	2		2		5	<1
Pruritus	4		1		5	
Erythema	5		5		1	
General						
Fatigue	54	7	49	5	61	9
Anorexia	19	1	9	< 1	27	1
Headache	19	2	17	4	23	4
Weakness	3	2	3	1	7	2
Dizziness	4	1	4		5	
Gastrointestinal System						
Nausea	36	1	16	< 1	49	1
Vomiting	20	< 1	6	<1	29	2
Constipation	18	1	6		22	
Diarrhea	6		3		10	1
Stomatitis	7		5	< 1	9	1
Abdominal Pain	2	< 1	1		5	< 1
Eye						
Vision Blurred	9	1	9	1	8	
Injury						
Radiation Injury NOS	7		4	< 1	2	
Central and Peripheral Nervous System						
Convulsions	6	3	7	3	11	3
Memory Impairment	3	< 1	4	< 1	7	1
Confusion	4	1	4	2	5	2
Special Senses Other						
Taste Perversion	6		2		5	
Respiratory System						
Coughing	5	1	1		8	< 1
Dyspnea	4	2	3	1	5	< 1
Psychiatric						
Insomnia	5		3	< 1	4	
Immune System						
Allergic Reaction	5		2	< 1	3	
Platelet, Bleeding and Clotting						
Thrombocytopenia	4	3	1		8	4
Musculoskeletal System						
Arthralgia	2	< 1	1		6	

*One patient who was randomized to RT only arm received RT+temozolomide. RT+TMZ=radiotherapy plus temozolomide; NOS=not otherwise specified.

Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥3 column.

Myelosuppression (neutropenia and thrombocytopenia), which is a known dose-limiting toxicity for most cytotoxic agents, including temozolomide, was observed. When laboratory abnormalities and adverse reactions were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic reactions were observed in 8% of the patients, and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic reactions, were observed in 14% of the patients treated with temozolomide.

Refractory Anaplastic Astrocytoma: Tables 8 and 9 show the incidence of adverse reactions in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these reactions should be attributed to temozolomide or the patients' underlying conditions,

but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug-related. The most frequently occurring adverse reactions were nausea, vomiting, headache, and fatigue. The adverse reactions were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse reaction. It usually occurred within the first few cycles of therapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range: 21 to 40 days) and 28 days for neutrophils (range: 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir, which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC<500 cells/ μ L) and thrombocytopenia (<20,000 cells/ μ L) in women than men in the first cycle of therapy (12% vs. 5% and 9% vs. 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

TABLE 8: Adverse Reactions in the Anaplastic Astrocytoma Trial in Adults (\geq 5%)

	No. (%) of Temozolomide Patients	
	(N=158)	
	All Reactions	Grade 3/4
Any Adverse Reaction	153 (97)	79 (50)
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)

Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision abnormal*	8 (5)	

*Blurred vision; visual deficit; vision changes; vision troubles

TABLE 9: Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma

Trial in Adults

	Temozolomide*
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

Temozolomide for injection delivers equivalent temozolomide dose and exposure to both temozolomide and 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC) as the corresponding temozolomide capsules. Adverse reactions probably related to treatment that were reported from the 2 studies with the intravenous formulation (n=35) that were not reported in studies using the temozolomide capsules were: pain, irritation, pruritus, warmth, swelling, and erythema at infusion site as well as the following adverse reactions: petechiae and hematoma.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of temozolomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

Dermatologic disorders: Toxic epidermal necrolysis and Stevens-Johnson syndrome.

Immune system disorders: Allergic reactions, including anaphylaxis. Erythema multiforme, which resolved after discontinuation of temozolomide and, in some cases, recurred upon rechallenge.

Hematopoietic disorders: Prolonged pancytopenia, which may result in aplastic anemia and fatal outcomes [see *Warnings and Precautions (5.1)*].

Hepatobiliary disorders: Fatal and severe hepatotoxicity, elevation of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis [see *Warnings and Precautions (5.5)*].

Infections and infestations: Opportunistic infections including Pneumocystis pneumonia (PCP) [see *Warnings and Precautions (5.3)*], primary and reactivated cytomegalovirus (CMV), and reactivation of hepatitis B infections including some cases with fatal outcomes.

Pulmonary disorders: Interstitial pneumonitis, pneumonitis, alveolitis, and pulmonary fibrosis.

Endocrine disorders: Diabetes insipidus.

7 DRUG INTERACTIONS

- Valproic acid: decreases oral clearance of temozolomide. (7.1)

7.1 Valproic Acid

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. See Warnings and Precautions section.

Temozolomide can cause fetal harm when administered to a pregnant woman. Five consecutive days of oral temozolomide administration of 0.38 and 0.75 times the highest recommended human dose (75 and 150 mg/m²) in rats and rabbits, respectively, during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. Doses equivalent to 0.75 times the highest recommended human dose (150 mg/m²) caused embryoletality in rats and rabbits as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for temozolomide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of temozolomide to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Temozolomide capsules have been studied in 2 open-label studies in pediatric patients (aged 3 to 18 years) at a dose of 160 to 200 mg/m² daily for 5 days every 28 days. In one trial, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All patients had recurrence following surgery and radiation therapy, while 31% also had disease progression following chemotherapy. In a second study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including patients with medulloblastoma/PNET (29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The temozolomide toxicity profile in pediatric patients is similar to adults. **Table 10** shows the adverse reactions in 122 children in the COG study.

TABLE 10: Adverse Reactions Reported in the Pediatric Cooperative Group Trial (≥10%)

	No. (%) of Temozolomide Patients (N=122)*	
Body System/Organ Class	All Reactions	Grade 3/4
Adverse Reaction		
Subjects Reporting an AE	107 (88)	69 (57)
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Thrombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neutropenia	62 (51)	24 (20)

*These various tumors included the following: PNET-medulloblastoma, glioblastoma, low grade astrocytoma, brain stem tumor, ependymoma, mixed glioma, oligodendroglioma, neuroblastoma, Ewing's sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofibrosarcoma, optic glioma, and osteosarcoma.

8.5 Geriatric Use

Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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 (2/8; 25%, $P=0.31$ and 2/10; 20%, $P=0.09$, respectively) in the first cycle of therapy than patients under 70 years of age [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

In newly diagnosed patients with glioblastoma multiforme, the adverse reaction profile was similar in younger patients (<65 years) vs. older (≥ 65 years).

8.6 Renal Impairment

Caution should be exercised when temozolomide is administered to patients with severe renal impairment [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

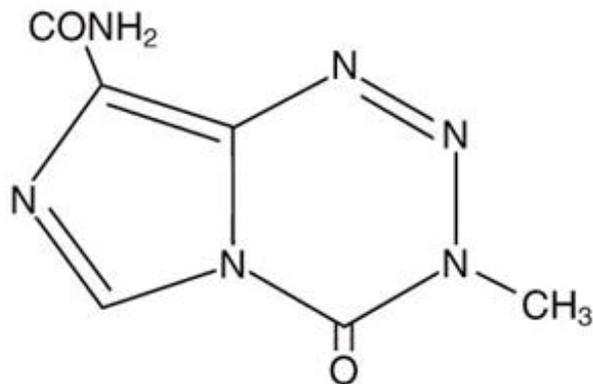
Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Doses of 500, 750, 1000, and 1250 mg/m² (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days), with adverse reactions reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

11 DESCRIPTION

Temozolomide capsules contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1d]-as-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence temozolomide can be administered orally and intravenously. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazene-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Temozolomide Capsules:

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients for temozolomide capsules are as follows: colloidal silicon dioxide, ethyl alcohol, lactose anhydrous, sodium starch glycolate, stearic acid and tartaric acid.

The body of the capsules are made of gelatin and titanium dioxide, and are white opaque color. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains alcohol, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, iron oxide black, n-butyl alcohol, propylene glycol and shellac.

Temozolomide Capsules 5 mg: The green cap contains FD&C Blue #2, gelatin, titanium dioxide and yellow iron oxide.

Temozolomide Capsules 20 mg: The yellow cap contains D&C Yellow #10, FD&C Yellow #6, gelatin and titanium dioxide.

Temozolomide Capsules 100 mg: The pink cap contains FD&C Blue #1, FD&C Red #3, FD&C Red #40, gelatin and titanium dioxide.

Temozolomide Capsules 140 mg: The blue cap contains FD&C Blue #1, gelatin and titanium dioxide.

Temozolomide Capsules 180 mg: The red cap contains FD&C Blue #1, FD&C Red #40, gelatin and titanium dioxide.

Temozolomide Capsules 250 mg: The white cap contains gelatin and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazene-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 O⁶ and N⁷ positions of guanine.

12.3 Pharmacokinetics

Absorption: Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median T_{max}

increased by 2-fold (from 1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Following a single oral dose of 150 mg/m², the geometric mean C_{max} values for temozolomide and MTIC were 7.5 mcg/mL and 282 ng/mL, respectively. Following a single oral dose of 150 mg/m², the geometric mean AUC values for temozolomide and MTIC were 23.4 mcg·hr/mL and 864 ng·hr/mL, respectively.

Distribution: Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.

Excretion: About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m². Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m²/day.

Effect of Age: A population pharmacokinetic analysis indicated that age (range: 19 to 78 years) has no influence on the pharmacokinetics of temozolomide.

Effect of Gender: A population pharmacokinetic analysis indicated that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men.

Effect of Race: The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use: A population pharmacokinetic analysis indicated that the oral clearance of temozolomide is similar in smokers and nonsmokers.

Effect of Renal Impairment: A population pharmacokinetic analysis indicated that creatinine clearance over the range of 36 to 130 mL/min/m² has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CL_{cr} <36 mL/min/m²). Caution should be exercised when temozolomide is administered to patients with severe renal impairment [see Use in Special Populations (8.6)]. Temozolomide has not been studied in patients on dialysis.

Effect of Hepatic Impairment: A study showed that the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment [see Use in Specific Populations (8.7)].

Effect of Other Drugs on Temozolomide Pharmacokinetics: In a multiple-dose study, administration of temozolomide capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5% [see *Drug Interactions (7.1)*].

A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H₂-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25 to 125 mg/m²) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and hardierian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolomide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolomide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at 0.25 and 0.63 times the maximum recommended human dose (50 and 125 mg/m²) in rats and dogs, respectively, and testicular atrophy in dogs at 0.63 times the maximum recommended human dose (125 mg/m²).

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration, and necrosis of the retina at temozolomide doses equal to or greater than 0.63 times the maximum recommended human dose (125 mg/m²). These changes were most commonly seen at doses where mortality was observed.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Glioblastoma Multiforme

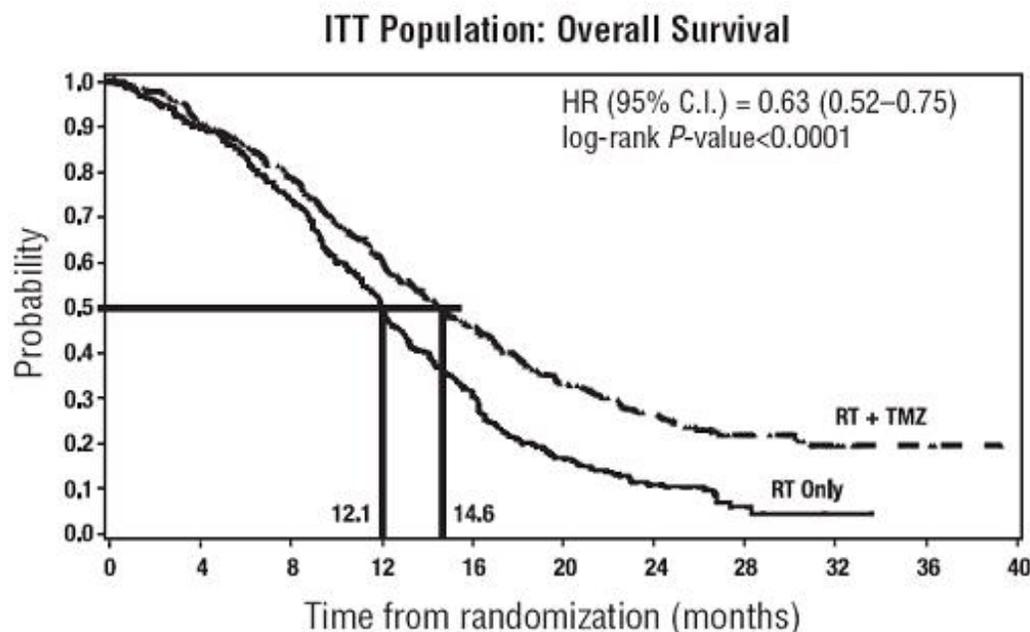
Five hundred and seventy-three patients were randomized to receive either temozolomide (TMZ)+Radiotherapy (RT) (n=287) or RT alone (n=286). Patients in the temozolomide+RT arm received concomitant temozolomide (75 mg/m²) once daily, starting the first day of RT until the last day of RT. for 42 days (with a maximum of 49

starting the first day of RT until the last day of RT, for 12 days (with a maximum of 10 days). This was followed by 6 cycles of temozolomide alone (150 or 200 mg/m²) on Days 1 to 5 of every 28-day cycle, starting 4 weeks after the end of RT. Patients in the control arm received RT only. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT includes the tumor bed or resection site with a 2- to 3- cm margin. *Pneumocystis pneumonia* (PCP) prophylaxis was required during the TMZ + RT, regardless of lymphocyte count, and was to continue until recovery of lymphocyte count to less than or equal to Grade 1.

At the time of disease progression, temozolomide was administered as salvage therapy in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277 (22%) in the temozolomide+RT arm.

The addition of concomitant and maintenance temozolomide to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement in overall survival compared to radiotherapy alone (**Figure 1**). The hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52 to 0.75) with a log-rank $P<0.0001$ in favor of the temozolomide arm. The median survival was increased by 2.5 months in the temozolomide arm.

FIGURE 1: Kaplan-Meier Curves for Overall Survival (ITT Population)



14.2 Refractory Anaplastic Astrocytoma

A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine, and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of >80. Sixty-three percent of patients had surgery other than a

biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

Temozolomide capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was $\geq 1.5 \times 10^9$ /L (1500/ μ L) and the nadir and Day 29, Day 1 of next cycle platelet count was $\geq 100 \times 10^9$ /L (100,000/ μ L), the temozolomide dose was increased to 200 mg/m²/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population, the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range: 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range: 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% CI: 31% to 58%) and progression-free survival at 12 months was 29% (95% CI: 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% CI: 62% to 86%) and 12-month overall survival was 65% (95% CI: 52% to 78%). Median overall survival was 15.9 months.

15 REFERENCES

1. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
2. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
3. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.[3]
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

Care should be exercised in the handling and preparation of temozolomide. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the contents to avoid inhalation or contact with the skin or mucous membranes. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the capsules. Procedures for proper handling and disposal of anticancer drugs should be considered¹⁻⁴. Several guidelines on this subject have been published.

16.2 How Supplied

Temozolomide capsules **5 mg** are supplied as size “3” hard gelatin capsules with green

opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “801” with black ink.

Temozolomide capsules **20 mg** are supplied as size “2” hard gelatin capsules with yellow opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “802” with black ink. They are available as follows:

NDC 50268-761-12 (5 capsules per card, 4 cards per carton).

Temozolomide capsules **100 mg** are supplied as size “1” hard gelatin capsules with pink opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “803” with black ink. They are available as follows:

NDC 50268-762-12 (5 capsules per card, 4 cards per carton).

Temozolomide capsules **140 mg** are supplied as size “0” hard gelatin capsules with blue opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “804” with black ink.

They are available as follows:

NDC 50268-763-12 (5 capsules per card, 4 cards per carton).

Temozolomide capsules **180 mg** are supplied as size “0” hard gelatin capsules with red opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “805” with black ink.

Temozolomide capsules **250 mg** are supplied as size “0” hard gelatin capsules with white opaque color caps imprinted “AMNEAL” and white opaque color bodies imprinted “806” with black ink.

16.3 Storage

Store temozolomide capsules at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

17.1 Information for the Patient

Physicians should discuss the following with their patients:

- Nausea and vomiting are the most frequently occurring adverse reactions. Nausea and vomiting are usually either self-limiting or readily controlled with standard antiemetic therapy.
- Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes.
- The medication should be kept away from children and pets.

Manufactured for:

AvKARE, Inc.

Pulaski, TN 38478

- Mfg. Rev. 01-2016-03
AV 09/16 (P)
AvPAK

PATIENT INFORMATION

Temozolomide (TEM-oh-ZOE-loe-mide) Capsules

What is the most important information I should know about temozolomide?

- **Temozolomide may cause birth defects.** Male and female patients who take temozolomide should use effective birth control. Female patients and female partners of male patients should avoid becoming pregnant while taking temozolomide.

See the section “What are the possible side effects of temozolomide?” for more information about side effects.

What is temozolomide?

Temozolomide is a prescription medicine used to treat adults with certain brain cancer tumors. Temozolomide blocks cell growth, especially cells that grow fast, such as cancer cells. Temozolomide may decrease the size of certain brain tumors in some patients.

It is not known if temozolomide is safe and effective in children.

Who should not take temozolomide?

Do not take temozolomide if you:

- have had an allergic reaction to dacarbazine (DTIC), another cancer medicine.
- have had a red itchy rash, or a severe allergic reaction, such as trouble breathing, swelling of the face, throat, or tongue, or severe skin reaction to temozolomide or any of the ingredients in temozolomide capsules. If you are not sure, ask your doctor. See the end of the leaflet for a list of ingredients in temozolomide capsules.

What should I tell my doctor before taking temozolomide?

Tell your doctor about all your medical conditions, including if you:

- are allergic to dacarbazine (DTIC) or have had a severe allergic reaction to temozolomide. See “Who should not take temozolomide?”

- have kidney problems
- have liver problems
- are pregnant. See “What is the most important information I should know about temozolomide?”
- are breast-feeding. It is not known whether temozolomide passes into breast milk. You and your doctor should decide if you will breast-feed or take temozolomide. You should not do both without talking with your doctor.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take a medicine that contains valproic acid (Stavzor[®], Depakene[®]).

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take temozolomide?

Temozolomide may be taken by mouth as a capsule at home.

There are two common dosing schedules for taking temozolomide.

- Some people take temozolomide for 42 days in a row (possibly 49 days depending on side effects) with radiation treatment. This is one cycle of treatment. After this, you may have “maintenance” treatment. Your doctor may prescribe 6 more cycles of temozolomide. For each of these cycles, you take temozolomide one time each day for 5 days in a row and then you stop taking it for the next 23 days. This is a 28-day maintenance treatment cycle.
- Another way to take temozolomide is to take it one time each day for 5 days in a row only, and then you stop taking it for the next 23 days. This is one cycle of treatment (28 days). Your doctor will watch your progress on temozolomide and decide how long you should take it. You might take temozolomide until your tumor gets worse or for possibly up to 2 years.
- Your dose is based on your height and weight, and the number of treatment cycles will depend on how you respond to and tolerate this treatment.
- Your doctor may modify your schedule based on how you tolerate the treatment.
- If your doctor prescribes a treatment regimen that is different from the information in this leaflet, make sure you follow the specific instructions given to you by your doctor.

Temozolomide Capsules:

- Take temozolomide capsules exactly as prescribed.
- Temozolomide capsules come in different strengths. Each strength has a different color cap. Your doctor may prescribe more than one strength of temozolomide capsules for you, so it is important that you understand how to take your medicine the right way. Be sure that you understand exactly how many capsules you need to take on each day of your treatment, and what strengths to take. This may be different whenever you start a new cycle.
- Talk to your doctor before you take your dose if you are not sure how much to take. This will help to prevent taking too much temozolomide and decrease your chances of getting serious side effects.
- Take each day’s dose of temozolomide capsules at one time, with a full glass of water.
- **Swallow temozolomide capsules whole. Do not chew, open, or split the**

capsules.

- If temozolomide capsules are accidentally opened or damaged, be careful not to breathe in (inhale) the powder from the capsules or get the powder on your skin or mucous membranes (for example, in your nose or mouth). If contact with any of these areas happens, flush the area with water.
- If you vomit temozolomide capsules, do not take any more capsules. Wait and take your next planned dose.
- The medicine is used best by your body if you take it at the same time every day in relation to a meal.
- To lessen nausea, try to take temozolomide on an empty stomach or at bedtime. Your doctor may prescribe medicine to prevent or treat nausea, or other medicines to lessen side effects with temozolomide.
- See your doctor regularly to check your progress. Your doctor will check you for side effects that you might not notice.
- If you miss a dose of temozolomide, talk with your doctor for instructions about when to take your next dose of temozolomide.
- Call your doctor right away if you take more than the prescribed amount of temozolomide. It is important that you do not take more than the amount of temozolomide prescribed for you.

What should I avoid while taking temozolomide?

- Female patients and female partners of male patients should avoid becoming pregnant while taking temozolomide. See “What is the most important information I should know about temozolomide?”

What are the possible side effects of temozolomide?

Temozolomide can cause serious side effects.

- See “What is the most important information I should know about temozolomide?”
- **Decreased blood cells.** Temozolomide affects cells that grow rapidly, including bone marrow cells. This can cause you to have a decrease in blood cells. Your doctor can monitor your blood for these effects.
 - -White blood cells are needed to fight infections. Neutrophils are a type of white blood cell that help prevent bacterial infections. Decreased neutrophils can lead to serious infections that can lead to death. Other white blood cells called lymphocytes may also be decreased.
 - -Platelets are blood cells needed for normal blood clotting. Low platelet counts can lead to bleeding. Tell your doctor about any unusual bruising or bleeding.

Your doctor will check your blood regularly while you are taking temozolomide to see if these side effects are happening. Your doctor may need to change the dose of temozolomide or when you get it depending on your blood cell counts. People who are age 70 or older and women may be more likely to have their blood cells affected.

- ***Pneumocystis Pneumonia (PCP).*** PCP is an infection that people can get when their immune system is weak. Temozolomide decreases white blood cells, which makes your immune system weaker and can increase your risk of getting PCP. **All patients** taking temozolomide will be watched carefully by their doctor for this infection, especially patients who take steroids. Tell your doctor if you have any of the following signs and symptoms of PCP infection: shortness of breath and/or fever, chills, dry cough.
- **Secondary cancers.** Blood problems such as myelodysplastic syndrome and

secondary cancers, such as a certain kind of leukemia, can happen in people who take temozolomide. Your doctor will watch you for this.

- **Convulsions.** Convulsions may be severe or life-threatening in people who take temozolomide.
- **Liver side effects** have been reported, which very rarely included death.
- Common side effects with temozolomide include:
 - nausea and vomiting. Your doctor can prescribe medicines that may help reduce these symptoms.
 - headache
 - feeling tired
 - loss of appetite
 - hair loss
 - constipation
 - bruising
 - rash
 - paralysis on one side of the body
 - diarrhea
 - weakness
 - fever
 - dizziness
 - coordination problems
 - viral infection
 - sleep problems
 - memory loss
 - pain, irritation, itching, warmth, swelling or redness at the site of infusion
 - bruising or small red or purple spots under the skin

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with temozolomide. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store temozolomide capsules?

- Store temozolomide capsules at 77°F (controlled room temperature). Storage at 59° to 86°F (15° to 30°C) is permitted occasionally.
- **Keep temozolomide capsules out of the reach of children and pets.**

General information about temozolomide.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use temozolomide for a condition for which it was not prescribed. Do not give temozolomide to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about temozolomide. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about temozolomide that is written for health professionals.

For more information, go to www.avkare.com or call 1-855-361-3993.

How are temozolomide capsules supplied?

Temozolomide capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. The capsules are available in six different strengths.

Temozolomide Capsule Strength Color

5 mg Green Cap

20 mg Yellow Cap

100 mg Pink Cap

140 mg Blue Cap

180 mg Red Cap

250 mg White Cap

What are the ingredients in temozolomide capsules?

Active ingredient: temozolomide.

Inactive ingredients: colloidal silicon dioxide, ethyl alcohol, lactose anhydrous, sodium starch glycolate, stearic acid and tartaric acid.

The body of the capsules are made of gelatin and titanium dioxide and are opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains alcohol, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, iron oxide black, n-butyl alcohol, propylene glycol and shellac.

Temozolomide Capsules **5 mg**: The green cap contains FD&C Blue #2, gelatin, titanium dioxide and yellow iron oxide.

Temozolomide Capsules **20 mg**: The yellow cap contains D&C Yellow #10, FD&C Yellow #6, gelatin and titanium dioxide.

Temozolomide Capsules **100 mg**: The pink cap contains FD&C Blue #1, FD&C Red #3, FD&C Red #40, gelatin and titanium dioxide.

Temozolomide Capsules **140 mg**: The blue cap contains FD&C Blue #1, gelatin and titanium dioxide.

Temozolomide Capsules **180 mg**: The red cap contains FD&C Blue #1, FD&C Red #40, gelatin and titanium dioxide.

Temozolomide Capsules **250 mg**: The white cap contains gelatin and titanium dioxide.

*The trademarks depicted in this piece are owned by their respective companies.

Manufactured for:

AvKARE, Inc.

Pulaski, TN 38478Mfg. Rev. 10-2015-01

AV 09/16 (P)

AvPAK

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 50268-761-12
Temozolomide Capsules
20 mg
For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose
5026876112

NDC 50268-761-12
Temozolomide Capsules
20 mg
For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose
5026876112

Each capsule contains: 20 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of varying capsule strengths in establishing a daily regimen.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant containers as defined in the USP.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

AvPAK
A Product of AvKARE
MFg. Rev. 10-2015-01 AV 09/16 (P)

NDC 50268-761-12

Temozolomide Capsules

20 mg

For Oral Administration
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Mfg. Rev. 10-2015-01

AV 09/16 (P)

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 50268-762-12

Temozolomide Capsules

100 mg

For Oral Administration

Cytotoxic - Read accompanying directions carefully

Rx Only

20 Capsules (4 x 5) Unit Dose

5026876212

NDC 50268-762-12
Temozolomide Capsules
100 mg
For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose
5026876212

Each capsule contains: 100 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of varying capsule strengths in establishing a daily regimen.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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NDC 50268-762-12

Temozolomide Capsules

100 mg

For Oral Administration
Cytotoxic - Read accompanying directions carefully

Rx Only
20 Capsules (4 x 5) Unit Dose



5026876212

NDC 50268-762-12

Temozolomide Capsules

100 mg

For Oral Administration
Cytotoxic - Read accompanying directions carefully

Rx Only
20 Capsules (4 x 5) Unit Dose



5026876212

Each capsule contains: 100 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of varying capsule strengths in establishing a daily regimen.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant containers as defined in the USP.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478



Mfg. Rev. 10-2015-01

AV 09/16 (P)

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 50268-763-12

Temozolomide Capsules

140 mg

For Oral Administration

Cytotoxic - Read accompanying directions carefully

Rx Only

20 Capsules (4 x 5) Unit Dose

5026876312

NDC 50268-763-12
Temozolomide Capsules
140 mg
For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose
5026876312

Each capsule contains: 140 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of varying capsule strengths in establishing a daily regimen.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant containers as defined in the USP.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

AvPAK
A Product of AvKARE
Mfg Rev. 10-2015-01 AV 09/16 (P)

NDC 50268-763-12

Temozolomide Capsules

140 mg

For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose



5026876312

NDC 50268-763-12

Temozolomide Capsules

140 mg

For Oral Administration
Cytotoxic - Read accompanying directions carefully
Rx Only
20 Capsules (4 x 5) Unit Dose



5026876312

Each capsule contains: 140 mg temozolomide.

Usual Dose: See package insert for recommendations regarding the use of varying capsule strengths in establishing a daily regimen.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant containers as defined in the USP.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478



Mfg. Rev. 10-2015-01

AV 09/16 (P)

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-761(NDC:65162-802)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
TARTARIC ACID (UNII: W4888I119H)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALCOHOL (UNII: 3K9958V90M)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	yellow (opaque) , white (opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	AMNEAL;802
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-761-12	20 in 1 BOX, UNIT-DOSE	03/23/2017	
1	NDC:50268-761-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203691	03/23/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-762(NDC:65162-803)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	100 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
TARTARIC ACID (UNII: W4888I119H)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALCOHOL (UNII: 3K9958V90M)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B71O)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	

Product Characteristics

Color	white (opaque) , pink (opaque)	Score	no score
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	AMNEAL;803
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-762-12	20 in 1 BOX, UNIT-DOSE	03/23/2017	
1	NDC:50268-762-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203691	03/23/2017	

TEMOZOLOMIDE

temozolomide capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50268-763(NDC:65162-804)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TEMOZOLOMIDE (UNII: YF1K15M17Y) (TEMOZOLOMIDE - UNII:YF1K15M17Y)	TEMOZOLOMIDE	140 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STEARIC ACID (UNII: 4ELV7Z65AP)	
TARTARIC ACID (UNII: W4888I119H)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
ALCOHOL (UNII: 3K9958V90M)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
BUTYL ALCOHOL (UNII: 8PJ61P6TS3)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SHELLAC (UNII: 46N107B710)	

Product Characteristics

Color	white (opaque) , blue (opaque)	Score	no score
Shape	CAPSULE	Size	22mm
Flavor		Imprint Code	AMNEAL;804
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50268-763-12	20 in 1 BOX, UNIT-DOSE	03/23/2017	07/31/2021
1	NDC:50268-763-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203691	03/23/2017	07/31/2021

Labeler - AvPAK (832926666)

Revised: 1/2024

AvPAK