TEMOTIZ 5/20/100/140/180/250

Temozolomide Capsules USP 5 mg/ 20 mg/ 100 mg/ 140 mg/ 180 mg/ 250 mg

Rx only

COMPOSITION

TEMOTIZ 5

Temozolomide Capsules USP 5 mg
Each Capsule contains:

Temozolomide	USP	5 mg
Excipients		q.s.

Colour: Approved colours used in capsule shell

TEMOTIZ 20

Temozolomide Capsules USP 20 mg
Each Capsule contains:

Temozolomide	USP	20 mg
Excipients		q.s.

Colour: Approved colours used in capsule shell

TEMOTIZ 100

Temozolomide Capsules USP 100 mg
Each Capsule contains:

Temozolomide	USP	100 mg
Excipients		q.s.

Colour: Approved colours used in capsule shell

TEMOTIZ 140

Temozolomide Capsules USP 140 mg
Each Capsule contains:

Temozolomide	USP	140 mg
Excipients q.s.		

Colour: Approved colours used in capsule shell

TEMOTIZ 180

Temozolomide Capsules USP 180 mg
Each Capsule contains:

Temozolomide	USP	180 mg
Excipients		q.s.

Colour: Approved colours used in capsule shell

TEMOTIZ 250

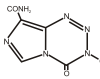
Temozolomide Capsules USP 250 mg
Each Capsule contains:

Temozolomide	USP	250 mg
Excipients		q.s.

Colour: Approved colours used in capsule shell

DESCRIPTION

TEMOTIZ contains Temozolomide, an imidazotetrazine derivative. The chemical name of TEMOTIZ is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]- as-tetrazine-8-carboxamide.



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 TEMOTIZ can be administered orally. The prodrug, Temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

CLINICAL PHARMACOLOGY

Mechanism of Action: TEMOTIZ is not directly active but undergoes rapid nonenzymatic conversion at physiologic thought to be primarily due to alkylation of DNA. Alkylation (methylation) occure mainly at the O_6 and N_7 positions of guanine.

Pharmacokinetics

Absorption: TEMOTIZ 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 TEMOTIZ 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 TEMOTIZ was administered after a modified high-fat breakfast. TEMOTIZ is rapidly eliminate with a Mean Elimination Half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range.

Distribution: TEMOTIZ 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: TEMOTIZ is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to TEMOZIT acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is know 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 TEMOTIZ 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%), about 5.5L/hr/m^2, 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/m^2/day.

INDICATIONS AND USAGE

TEMOTIZ capsule is indicated for the treatment of adult patients with newly diagnosed gliblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. Temozolomide capsule is 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.

CONTRAINDICATIONS

TEMOTIZ 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 capsule is also contraindicated in patients who have a history of hypersensitivity to dacarbazine (DTIC), since both drugs are metabolized to 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC).

WARNINGS

Patients treated with TEMOTIZ may experience myelosuppression, including prolongedd pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concemitant complicated assessment. Prior to dosing, patients mst have an absolute neutrophil count (ANC) greater than or equal to 1.5 x 10^9/L and a platelet count greater than or equal to 100 z 10^9/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 x 10^9/L and platelet count exceeds 100 x 10^9/L. Geriatric patients and women have been shown in clinical trails to have a higher risk of developing myelosuppression.

Very rare Cases of myelodysplstic syndrome and secondary malignancies, including myeloid leukemia, have been observed.

Pneumocystis pneumonia (PCP) is required for all patients receiving concomitant Temozolomide and radiotherapy for the 42-day regimen.

Pregnancy: TEMOTIZ can cuse fetal harm when administered to a pregnant women. Administration of TEMOTIZ to rats and rabbits during organogenesis at 0.38 and 0.75 times the maximum recommended human dose (75 and 150 mg/m^2), respectively, caused numerous fetal malformations of the external organs, soft tissues, and skeleton in both species.

PRECAUTIONS

Information for Patients: Nausea and Vomiting were among the most frequently occurring adverse events. These were 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.

Drug Interactions: Administration of valproic acid decreases oral clearance of TEMOTIZ by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment: Caution should be excersiced when Temozolomide capsules are administered to patients with severe Hepatic or renal impairment.

Geriatrics: Clinical studies of TEMOTIZ 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; P=0.09, respectively) in the first cycle of therapy than patients under 70 years of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility: TEMOTIZ is carcinogenic in rats at doses less than the maximum recommended human dose. TEMOTIZ induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25 to 125 mg/m^2) 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, schwnnomas of the heart, optic nerve, and harderian 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.

Pregnancy Category D

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 TEMOTIZ to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. TEMOTIZ 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/m^2 daily for 5 days every 28 days. In one trail, 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 TEMOTIZ toxicity profile in pediatric patients is similar to adults. Table 1 shows the adverse reactions in 122 children in the COG study.

Size: 100x182 mm

Table 1		
Adverse Events Reported in Pediatric Cooperative Group Trail(>10%)		
	No. (%) of TEMOTIZ Patients (N=122)a	
Body System/ Organgan Adverse Event	**All Events**	**Gr 3/4**
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)

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

ADVERSE REACTIONS IN ADULTS:

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

Myelosuppression (neutropenia and thrombocytopenia), which is a know dose-limiting toxicity for most cytotyxic 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 TEMOTIZ.

Number (%) of Patients with Adverse Reactions: All and Severe/Life Threatening (Incidence of 5% or Greater)												
	Concomitant Phase RT Alone (n = 285)				Concomitant Phase RT + TMZ (n = 288)a				Maintenance Phase TMZ (n = 224)			
	All		Grade ≥3		All		Grade ≥3		All		Grade ≥3	
Subjects Reporting any Adverse Reaction	**258**	**(91)**	**74**	**(26)**	**266**	**(92)**	**80**	**(28)**	**206**	**(92)**	**82**	**(37)**
Body as a Whole – General Disorders												
Anorexia	25	(9)	1	(<1)	56	(19)	2	(1)	61	(27)	3	(1)
Dizziness	10	(4)	0		12	(4)	2	(1)	12	(5)	0	
Fatigue	139	(49)	15	(5)	156	(54)	19	(7)	137	(61)	20	(9)
Headache	49	(17)	11	(4)	56	(19)	5	(2)	51	(23)	9	(4)
Weakness	9	(3)	3	(1)	10	(3)	5	(2)	16	(7)	4	(2)
Central and Peripheral Nervous System Disorders												
Confusion	12	(4)	6	(2)	11	(4)	4	(1)	12	(5)	4	(2)
Convulsions	20	(7)	9	(3)	17	(6)	10	(3)	25	(11)	7	(3)
Memory Impairment	12	(4)	1	(<1)	8	(3)	1	(<1)	16	(7)	2	(1)
Disorders of the Eye												
Vision Blurred	25	(9)	4	(1)	26	(9)	2	(1)	17	(8)	0	
Gastrointestinal System Disorder												
Abdominal Pain	2	(1)	0		7	(2)	1	(<1)	11	(5)	1	(<1)
Constipation	18	(6)	0		53	(18)	3	(1)	49	(22)	0	
Diarrhea	9	(3)	0		18	(6)	0		23	(10)	2	(1)
Nausea	45	(16)	1	(<1)	105	(36)	2	(1)	110	(49)	3	(1)
Stomatitis	14	(5)	1	(<1)	19	(7)	0		20	(9)	3	(1)
Vomiting	16	(6)	1	(<1)	57	(20)	1	(<1)	66	(29)	4	(2)
Injury and Poisoning	(6)	1	(<1)	57	(20)	1	(<1)	66	(29)	4	(2)	
Radiation Injury NOS	11	(4)	1	(<1)	20	(7)	0		5	(2)	0	
Musculoskeletal System Disorders												
Arthralgia	2	(1)	0		7	(2)	1	(<1)	14	(6)	0	
Platelet, Bleeding and Clotting Disorders												
Thromobocytopeina	3	(1)	0		11	(4)	8	(3)	19	(8)	8	(4)
Psychiatric Disorders												
Insomnia	9	(3)	1	(<1)	14	(5)	0		9	(4)	0	
Respiratory System Disorders												
Coughing	3	(1)	0		15	(5)	2	(1)	19	(8)	1	(<1)
Dyspnea	9	(3)	4	(1)	11	(4)	5	(2)	12	(5)	1	(<1)
Skin and Subcutaneous Tissue Disorders												
Alopecia	179	(63)	0		199	(69)	0		124	(55)	0	
Dry Skin	6	(2)	0		7	(2)	0		11	(5)	1	(<1)
Erythema	15	(5)	0		14	(5)	0		2	(1)	0	
Pruritus	4	(1)	0		11	(4)	0		11	(5)	0	
Rash	42	(15)	0		56	(19)	3	(1)	29	(13)	3	(1)
Special Senses Other, Disorders												
Taste Perversion	6	(2)	0		18	(6)	0		11	(5)	0	

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.

DOSAGE AND ADMINISTRATION

Dosage of TEMOTIZ 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.

Patients with Newly Diagnosed High Grade Glioma:

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 greater than or equal to 1.5 x 10^9/L (1500/mL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are greater than or equal to 100 x 10^9/L (100,000/mL), the TEMOTIZ capsules dose may be increased to 200 mg/m2/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 x 10^9/L (1500/mL) and the platelet count exceeds 100 x 10^9/L (100,000/mL).

The next cycle of TEMOTIZ capsules should not be started until the ANC and platelet count exceed these levels. If the ANC falls to less than 1.0 x 10^9L (1000/mL) or the platelet count is less than 50 x 10^9/L (50,000/mL) 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. TEMOTIZ 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.

In clinical trials, TEMOTIZ e capsules was administered under both fasting and nonfasting conditions; however, absorption is affected by food, and consistency of administration with respect to food is recommended. There are no dietary restrictions with TEMOTIZ capsules. To reduce nausea and vomiting, TEMOTIZ 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.

STORAGE

Store below 30°C.

SHELF LIFE

24 Months

HOW SUPPLIED

TEMOTIZ 5/20/100/140/180/250 mg supplied in bottle of 5 Capsules packed in a HDPE container

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited

Factory: Tukucha, Nala-1, Banepa, Nepal.

Regd. Office: Maligaun-5, Kathmandu, Nepal.