DOSAGE AND ADMINISTRATION

Dosage of Temozolomide 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: Temozolomide is administered at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance Temozolomide 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. Temozolomide 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 greater than or equal to 1.5 x 10^9 /L, platelet count greater than or equal to 100 x 10^9 /L, common toxicity criteria (CTC) nonhematological toxicity less than or equal to 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 and radiotherapy, and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC Grade less than or equal to 1)

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

Toxicity	Temozolomide Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	greater than or equal to 0.5 and less than 1.5 x 10^9 /L	less than 0.5 x 10^9 /L
Platelet Count	greater than or equal to 10 and less than 100 x 10^9 /L	less than 10 x 10^9 /L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

*Treatment with concomitant Temozolomide could be continued when all of the following conditions were met: absolute neutrophil count greater than or equal to 1.5 x 10^9 /L; platelet count greater than or equal to 100 x 10^9 /L; CTC nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting). CTC=Common Toxicity Criteria.

Maintenance Phase: Cycle 1: Four weeks after completing the TEMOZOLOMIDE+RT phase, Temozolomide is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. Cycles 2-6: At the start of Cycle 2, the dose can be escalated to 200 mg/m^2, if the CTC nonhematologic toxicity for Cycle 1 is Grade less than or equal to 2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is greater than or equal to 1.5 x 10^9 /L, and the platelet count is greater than or equal to 100 x 10^9 /L. The dose remains at 200 mg/m^2 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.

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 greater than or equal to 1.5 x 10^9 /L (1500/μL) 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/μL), the TEMOZOLOMIDE dose may be increased to 200 mg/m^2 /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/μL) and the platelet count exceeds 100 x 10^9 /L (100,000/μL). The next cycle of TEMOZOLOMIDE should not be started until the ANC and platelet count exceed these levels. If the ANC falls to less than 1.0 x 10^9 /L (1000/μL) or the platelet count is less than 50 x 10^9 /L (50,000/μL) 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. TEMOZOLOMIDE 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.

DOSE ADJUSTMENTS

Temozolomide doses must be adjusted according to nadir neutrophil and platelet counts. Subsequent doses may be increased to 200 milligrams per square meter per day (for 5 consecutive days in a 28 day treatment cycle) if the absolute neutrophil counts on both the nadir and the first day of the next dose cycle are above 1.5 x 10^9/litre (1500/microlitre) and platelet counts exceed 100 x 10^9/litre (100,000/microlitre).

If the absolute neutrophil count (ANC) falls to below 1x10^9/litre (1000/microlitre) and the platelets are less than 50 x 10^9/litre (50,000/microlitre), treatment should be withdrawn or postponed until recovery of ANC to greater than 1500/ microlitre and platelets to greater than 100,000/microlitre. Decrease the next dose by 50 milligrams per square meter, but not to less than total daily dose of 100 milligrams per square meter, the lowest recommended dose.

OVERDOSAGE

Doses of 500, 750, 1,000 and 1,250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at 1,000 mg/m^2 and at 1,250 mg/ m^2. Up to 1,000 mg/ m^2 has been taken as a single dose, with only the expected effects of neutropenia and thrombocytopenia resulting . In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

STORAGE

Store below 25°C. Protect from light and moisture. Keep out of reach of children

PRESENTATION

Strip of 5 Capsules and Jar of 5 Capsules.

Dec. 2016

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by
Getwell Pharmaceuticals
Vastrapur, Ahmedabad - 380015, Gujarat, INDIA.
At: 357, GIDC, Sachin, Surat, Gujarat, INDIA

0700DZM-DM1216-00

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Temozolomide Capsules IP

TEMZOL™

Rx only

WARNING

Patients treated with temozolomide may develop myelosuppression. The including of Myelosuppression was approximately three times higher in females. Prior to dosing, patients must have an absolute neutrophil count (ANC) ≥1.5 ^{9}/L and a platelet count ≥100 ×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 × 10^9/L and platelet count exceeds 100 × 10^9/L.

DESCRIPTION

Temozolomide capsules for oral administration contain temozolomide, an imidazotetrazine derivative.

COMPOSITION

TEMZOL™-20

Each hard gelatin capsule contains	
Temozolomide IP	20 mg
Excipients	q.s
Approved colour used in capsule shell.	

TEMZOL™-100

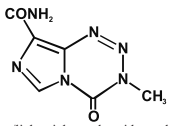
Each hard gelatin capsule contains	
Temozolomide IP	100 mg
Excipients	q.s
Approved colour used in capsule shell.	

TEMZOL™-250

Each hard gelatin capsule contains	
Temozolomide IP	250 mg
Excipients	q.s
Approved colour used in capsule shell.	

CHEMICAL STRUCTURE

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



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_8O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH(<5), and labile at pH>7, hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen1-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

Temozolomide spontaneously undergoes hydrolysis to active metabolite monomethyl triazeno imidazole carboxamide(MTIC) when in contact with slightly basic pH of blood & tissues. MTIC rapidly breaks down to form methyldiazoniumion primarily methylates guanine residues in the DNA molecule resulting in the formation of 0-6 and N-7 methyl guanine, which is responsible for cytotoxic effect of temozolomide.

PHARMACOKINETICS

Temozolomide is rapidly absorbed after oral administration and the bioavailability is 100 %. Absorption is reduced by approximately 9 % when taken with food, and is not clinically significant effect. However to reduce the potential for nausea and vomiting, it is recommended that patients take temozolomide at least 1hr before a meal or preferably at bed time. Peak plasma concentration is achieved in 1 hr. When temozolomide was administered after a modified high-fat breakfast, T_{max} increased to 2.3 h Temozolomide is completely absorbed orally, with peak serum concentrations occurring in 1 to 2 hours. In adults, the volume of distribution of temozolomide is 28 L and its total body clearance is approximately 100 mL/min/m^2. The drug is degraded in plasma and tissues to the cytotoxic monomethyl 5-triazino imidazole carboxamide (MTIC). Up to 15 % of a dose is excreted in the urine as unchanged drug. The elimination half-life of temozolomide is 1.8 hours. Clearance of temozolomide is approximately 5 % lower (adjusted for body surface area) in women than in men.

CLINICAL STUDIES

Yung WK et al in a multicenter, phase II trial enrolled 162 patients with malignant astrocytoma at first relapse. After central histologic review , 111 patients were confirmed to have had an anaplastic astrocytoma(AA) or anaplastic mixed oligoastrocytoma. Chemotherapy naive patients were treated with temozolomide 200 mg/m^2/d. Patients previously treated with chemotherapy received temozolomide 150 mg/ m^2/d; the dose could be increased to 200 mg/ m^2/d in the absence of grade ¾ toxicity. Therapy was administered orally on the first 5 days of a 28 day cycle. Progression free survival (PFS) at 6 months was 46 % (95 %) confidence interval, 38 % to 54 %). The median PFS was 5.4 months and PFS at 12 months was 24 %. The median overall survival was 13.6 months and the 6 and 12 months survival rates were 75% and 56% respectively. The objective response rate was 35 % (8 % complete response [CR], 27 % partial response [PR], with an additional 26 % of patients with stable disease (SD). The median PFS for patients with SD was 4.4 months, with 33 % progression free at 6 months. Adverse events were mild to moderate with hematologic side effects occurring in less than 10 % of patients.

INDICATION AND CLINICAL USES

Temozolomide capsules are indicated for the treatment of patients with anaplastic astrocytoma

at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. This indication is based on the response rate in the indicated population. There are no available results from randomized controlled trials in recurrent anaplastic astrocytoma that demonstrate a clinical benefit from treatment, such as improvement in disease related symptoms, delayed disease progression, or improved survival.

Temozolomide capsules are also used for the treatment patients with malignant glioma, such as glioblastoma multiforme, showing recurrence or progression after standard therapy.

CONTRAINDICATION

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-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC).

It is also contraindicated in pregnancy and lactation

ADVERSE EFFECTS

The most frequently occurring side effects are nausea, vomiting, headache and fatigue. The adverse events are usually NCI common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and are self limiting , with nausea and vomiting, readily controlled with an antiemetics.

Hematologic toxicities: Myelosuppression (thrombocytopenia and neutropenia) usually occurs within the first few cycles of therapy and is the dose-limiting adverse event. 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.

Gastrointestinal effects: Nausea and vomiting may occur in up to 75 % of patients. Mucositis, diarrhea, constipation, anorexia and stomatitis are described with administration of temozolomide. Nausea and vomiting may be reduced by taking temozolomide on an empty stomach.

Cardiovascular effects: Peripheral edema was reported in 11 % of patients receiving temozolomide in clinical trials.

Neurologic effects: Headache, fatigue, convulsions, paresis, hemiparesis, somnolence, dizziness, GIT disturbance, amnesia, paresthesia, ataxia and transient neurologic deterioration are described with the administration of temozolomide.

Psychiatric effects: Anxiety, depression and insomnia are described with the administration of temozolomide.

Endocrine effects: Ovarian suppression is described with the administration of temozolomide.
Electrolyte effects: Hypercalcemia is described with the administration of temozolomide.

Genitourinary effects: Testicular function may be affected by temozolomide therapy. Male patients should use effective methods of contraception while undergoing treatment.

Hepatic effects: Elevated hepatic enzymes are described with the administration of temozolomide.

Respiratory effects: Upper respiratory tract infections, including pharyngitis and sinusitis are described with the administration of temozolomide.

Dermatologic effects: Alopecia, rash and pruritus are described with administration of temozolomide.

	Very common (10% or more)	Common (1% to 10%)	Uncommon (0.1% to 1%)
Gastrointestinal	Constipation (Up to 33%), nausea (Up to 53%), vomiting (Up to 42%), diarrhea (16%)	Abdominal pain, diarrhea, stomatitis, taste perversion, dysphagia, dyspepsia	Abdominal distension, fecal incontinence, gastrointestinal disorder, gastroenteritis, haemorrhoids.
Nervous system	Headache (Up to 41%), convulsions (Up to 23%), hemiparesis (18%), abnormal coordination (11%)	Dizziness, confusion, memory impairment, amnesia, paresthesia, somnolence, paresis, urinary incontinence, ataxia, abnormal gait, neuropathy, balance impairment, speech disorder, tremors, hemiparesis	
Cardiovascular	Peripheral edema (11%)		Palpitation
Other	Fatigue (Up to 61%), asthenia (13%), fever (13%)	Weakness, radiation injury, face edema, pain, hearing impairment	Otitis media, tinnitus, hyperacusis, earache, deafness, vertigo, impotence, vaginal hemorrhage, menorrhagia, amenorrhea, vaginitis, breast pain.
Endocrine	Adrenal hypercorticism		
Respiratory	Cough, dyspnea, upper respiratory tract infection, pharyngitis, sinusitis		
Dermatologic	Alopecia (55 to 69%), rash (13 to 19%)	Dry skin, erythema, pruritus, petechiae	Photosensitivity reaction, abnormal pigmentation, sweating increased

Psychiatric		Insomnia, anxiety, depression	Agitation, apathy, behavior disorder, hallucination, amnesia
Metabolic	Anorexia (19 to 27%)	Weight increase, weight decrease, hyperglycemia	Hypokalemia.
Musculoskeletal		Arthralgia, back pain.	
Ocular		Vision blurred, diplopia	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain, dry eyes.
Immunologic		Infection, Herpes simplex, wound infection, candidiasis oral	Herpes zoster, influenza-like symptoms
Hematologic		Thrombocytopenia, hemorrhage, leukopenia, neutropenia, lymphopenia, febrile neutropenia, anemia	
Hepatic		ALT increased	Hepatic enzymes increased, Gamma GT increased, AST increased
Hypersensitivity		Allergic reaction	
Renal		Urinary tract infection, micturition increased frequency	Dysuria

WARNING AND PRECAUTIONS

WARNING

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) greater than or equal to 1.5×10^9/L and a platelet count greater than or equal to 100×10^9/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 1.5×10^9/L and platelet count exceeds 100×10^9/L. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

Myelodysplastic Syndrome

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

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.

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.

PRECAUTIONS

Fertility: Temozolomide can have genotoxic effects and may cause irreversible infertility in males. Men are advised not to father a child during or up to 6 months after treatment and to seek advice on cryopreservation of sperm prior to treatment.
Pregnancy: FDA Pregnancy Category D. Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well- controlled studies in pregnant woman. There is positive evidence of human fetal risk, but the benefits, from use in pregnant woman may be acceptable despite the risk (e.g., 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).
Administration of Temozolomide 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.
Breast feeding is not recommended due to the potential secretion into breast milk.

Laboratory tests: A complete blood count should be obtained on day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5×10^9/L and the platelet count falls below 100×10^9/L.

Mutagenicity and Carcinogenicity: Temozolomide is mutagenic in Ames test and clastogenic in mammalian in vitro mutation tests and is carcinogenic in rats.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

DRUG INTERACTION

In a separate phase I study, administration of Temozolomide with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).
Administration of Temozolomide with food resulted in a 33 % decrease in Cmax and a 9 % decrease in area under the curve (AUC). As it cannot be excluded that the change in Cmax is clinically significant, Temozolomide should be administered without food.
Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonists, or phenobarbital did not alter the clearance of Temozolomide.
No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other medicinal products. However, since Temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.
Use of Temozolomide in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.