Temozolomide Capsules I.P.

Composition

TEMOLOZ -250

Each Capsule contains:

Temozolomide I.P. 250 mg.

TEMOLOZ-100

Each Capsule contains

Temozolomide I.P. 100 mg.

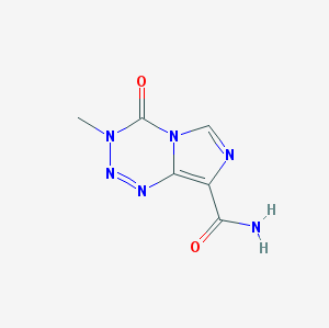
TEMOLOZ-20

Each Capsule contains

Temozolomide I.P. 20 mg.

Description

Temozolomide Capsules for oral administration contain Temozolomide, an imidazotetrazine derivative. 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 C6H6N6O2 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. The produg, 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: Temozzolomide is not directly active but undergoies rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to Alkylation of DNA. Alkylation (methylation) occurs at the O6 and O7 positions of guanine.

Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration, peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of Temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9% respectively, and T increased 2-fold (from 1.1 to 2.25 hours) when Temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

Hepatically Impaired Patients in a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Childs-pugh Class 1-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.

Drug-Drug Interactions in a multiple-dose study, administration of TEMOLOZ Capsules with Ranitidine did not change the C or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5% (See PRECAUTIONS)

Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Indications

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

TEMOLOZ 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 nitrosurea and procarbazine.

Dosage & Administration

Dosage of TEMOLOZ Capsules must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophill and plated counts at the time of initiating the next cylce.

Patients with newly diagnosed high grade glioma:

Concomitant Phase : TEMOLOZ is administered orally at 75 mg/m2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance TEMOLOZ for 6 cycles. Focal RT includes the tumor bed or resection site with a 2-3 cm margin. No dose reductions are

recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMOLOZ dose should be continued throughtout the 42 day concomitant period up to 49 days if all of the following conditions are met; absolute neutrophil count> 1.5 x 102/L platelet count> 100X102/L common toxicity criteria (CTC) non-hematological toxicity<Grade 1 (except for alopecia, nausea and vomiting.)

Maintenance Phase Cycle 1: Four weeks after completing the TEMOLOZ + RT PHASE, TEMOLOZ is 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 2-6 : At the start of Cycle 2, the dose is escalated to 200 mg/m2, if the CTC non-hematologic toxicity for Cycle 1 is Grade <2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is >1.5 x102/L, and the platelet count is >100x102/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 1 and 2.

Patients with refractory analplastic astrocytoma

For adults the initial dose is 150 mg/m2 orally once daily for 5 consecutive days per 28-days treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next

Table 1 Temozolomide Dose Levels for Maintenance Treatment.,

Dose Level	Dose mg/m2/day	Remarks
1	100	Reduction for Prior toxicity.
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity.

Table 2 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment.

Toxicity	Reduce TMZ by 1 Dose Level	Discontinue TMZ
Absolute Neutrophill Count	<1.0x 109/L	See footnote b
Platelet Count	<50x109/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4b.

a: TMZ dose level are listed in 6.

b: TMZ is to be discontinued if dose reduction to <100 mg/m2 is required or if the same Grade 3

non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ= temozolomide; CTC = Common Toxicity Criteria.

cycle) ANC are > 1.5x109/L (1,500/uL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are> 100x109/L (1,00,000/uL), the TEMOLOZ 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 1.5x109/L (50,000/uL) during any cycle, the next cycle should be reduced by 50 mg/m2, but not below 100 mg/m2, the lowest recommended dose. TEMOLOZ 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.

Handling and Disposal

TEMOLOZ causes the rapid appearance of malignant tumors in rats. 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 Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that allof the procedures recommended in the guidelines are necessary or appropriate.

Administration of TEMOLOZ

Patients should take each days with a full glass of water at the same time each day. Taking the medication on an empty stomach or at bedtime may help ease nausea. If patients are also taking antinausea or other medications to relieve the side effects associated with TEMOLOZ, they should be advised to take these medications 30 minutes before they take TEMOLOZ . Temozolomide causes the rapid appearance of malignant tumors in rats. Patients should not open or split the capsules. 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. The TEMOLOZ capsules should be swallowed whole and NEVER CHEWED.

WARNING:

Patients treated with TEMOLOZ Capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) > 1.5x109/L and Platelet count >100x109/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 109/L and platelet count exceeds 100 x 109/L. Geriatric patients and women have been shown in clinical trails to have a higher risk of developing myelosuppression. Very rare cases of yelodyspiastic syndrome and secondary malignacies, including myeloid leukemia have also been observed.

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against Pneumocystic carinii pneumonia is required for all patients receiving concomitant TEMOLOZ and radiotherapy for the 42 day regimen.

There may be a higher occurrence of PCP when temozolomide is administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy. or if the patients becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMOLOZ Capsules.

Precautions:

Patients with Severe Hepatic or Renal Impairment : Caution should be exercised when TEMOLOZ Capsules are administered to patients with severe hepatic or renal impairment.

Geriatrics

Caution should be exercised when treating elderly patients. In newly diagnosed patients with glioblastoma multiforme the adverse event profile was similar in younger patients (<65 years) vs older (>65 years)

Laboratory Tests

For the concomitant treatment phase with RT a complete blood count should be obtained weekly.

For the 28 day treatment cycles, 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 x 109/L and the platelet count falls below 100x109/L.

Carcinogenesis, Mutagenesis, and impairment of Fertility.

Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200mg /m2 temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found.

Temozolomide was mutagenic in Vitro in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte asays).

Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demostrated testicular toxicity (syncytial cells/immature sperm, testicular atophy) at doses of 50mg/m2 in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose or a body surface area basis).

Pregnancy Category D: See WARNING Section.

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 from TEMOLOZ Capsules, patients receiving TEMOLOZ should discontinue nursing.

PEDIATRIC USE

TEMOLOZ effectiveness in children has not been demostrated. The TEMOLOZ toxicity profile in children is similar to adults.

Adverse Reactions

Newly Diagnosed Glioblastoma Multiforme

During the concomitant phase (TEMOLOZ + radiotherapy), adverse events including Thrombocytopenia, nausea, vomiting, anorexia and constipation, were more frequent in the TEMOLOZ + RT arm the RT arm.

The incidence of other adverse events was comparable in the two arms. The most common adverse events across the cumulative TEMOLOZ experience were alopecia, nausea, vomiting, anorexia, headache, and constipation. Forty-nine percent (49%) of patients treated with TEMOLOZ reported one or more severe events, most commonly fatigue, convulsion, headache and thrombocytopenia. Overall, the pattern of events during the maintenance phase was consistent with the known safety profile of TEMOLOZ.

Drug Interactions

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

Overdosage: Doses of 500, 750, 1,000 and 1,250 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 it expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events 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 events 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 in needed. Supportive measures should be provided as necessary.

CONTRAINDICATIONS

TEMOLOZ (Temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of the components or DTIC, since both drugs are metabolized to MTIC.

Storage:

Store below 25°C. Protect from light & moisture.

Presentation :

Each bottle of TEMOLOZ -250 contains 5 capsules.

Each bottle of TEMOLOZ -100 contains 5 capsules

Each bottle of TEMOLOZ- 20 contains 5 capsules

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
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