141.0 mm

206.0 mm

Zolomid 100mg Capsule

(Temozolomide)

زولومڈ ۱۰۰ ملی گرام کیپسول

(ٹیمزولومائیڈ)

COMPOSITION

Zolomid Capsule 100mg

Each capsule contains:

Temozolomide.....100mg

(USP Specifications)

DESCRIPTION

ZOLOMID (Temozolomide) is an oral alkylating agent used for the treatment of refractory anaplastic astrocytoma -- a type of cancerous brain tumor. Temozolomide is not active until it is converted at physiologic pH to the active form, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC).

MECHANISM OF ACTION

Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-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.

INDICATIONS

Newly Diagnosed Glioblastoma Multiforme

ZOLOMID (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

Refractory Anaplastic Astrocytoma

ZOLOMID 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.

DOSAGE AND ADMINISTRATION

Refractory Anaplastic Astrocytoma:

Initial dose 150 mg/m2 once daily for 5 consecutive days per 28-day treatment cycle.

Adult patients with newly-diagnosed glioblastoma multiforme

75 mg/m^2 for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m2 once daily for Days 1-5 of a 28-day cycle of ZOLOMID for 6 cycles.

It means temozolomide is administered in combination with focal radiotherapy (concomitant phase) followed by up to 6 cycles of Temozolomide (TMZ) monotherapy (monotherapy phase).

Concomitant phase

TMZ is administered orally at a dose of 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of TMZ administration should be decided weekly according to haematological and non-haematological toxicity criteria. TMZ administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l
- Thrombocyte count ≥ 100 x 10^9/l
- Common toxicity criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TMZ administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Table 1. TMZ dosing interruption or discontinuation during concomitant radiotherapy and TMZ

Toxicity	TMZ interruption[a]	TMZ discontinuation
Absolute neutrophil count	≥ 0.5 and < 1.5 x 10^9/l	< 0.5 x 10^9/l
Thrombocyte count	≥ 10 and < 100 x 10^9/l	< 10 x 10^9/l
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

[a]: Treatment with concomitant TMZ can be continued when all of the following conditions are met:

Absolute neutrophil count ≥ 1.5 x 10^9/l; thrombocyte count ≥ 100 x 10^9/l; CTC non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).

Monotherapy phase

Four weeks after completing the TMZ + RT concomitant phase, TMZ is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 if the CTC non-hematological toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/l, and the thrombocyte count is ≥ 100 x 10^9/l. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions and discontinuations during the monotherapy 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 TMZ). The dose should be reduced or administration discontinued according to Table 3.

Table 2. TMZ dose levels for monotherapy treatment

Dose level	TMZ dose (mg/m^2/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 3. TMZ dose reduction or discontinuation during monotherapy treatment

Toxicity	Reduce TMZ by 1 dose level	Discontinue TMZ
Absolute neutrophil count	< 1.0 x 10^9/l	See footnote b
Thrombocyte count	< 50 x 10^9/l	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

[a]: TMZ dose levels are listed in Table 2.

[b]: TMZ is to be discontinued if:

- Dose level -1 (100 mg/m^2) still results in unacceptable toxicity
- The same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

Adult and Paediatric patients 3 years of age or older with recurrent or progressive malignant glioma

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, TMZ is administered orally at a dose of 200 mg/m^2 once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 once daily, for 5 days if there is no haematological toxicity.

Special populations

Paediatric population

In patients 3 years of age or older, TMZ is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited. The safety and efficacy of TMZ in children under the age of 3 years have not been established. No data are available.

Patients with hepatic or renal impairment

The pharmacokinetics of TMZ were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. No data are available on the administration of TMZ in patients with severe hepatic impairment (Child's Class C) or with renal impairment. Based on the pharmacokinetic properties of TMZ, it is unlikely that dose reductions are required in patients with severe hepatic impairment or any degree of renal impairment. However, caution should be exercised when TMZ is administered in these patients.

Elderly patients

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of TMZ is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia.

Method of administration

Temozolomide should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

PHARMACOKINETICS

Absorption: Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (Cmax) achieved in a median Tmax 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 Tmax increased by 2-fold (from 1-2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

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: 19-78 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 (CLcr <36 mL/min/m2). Caution should be exercised when ZOLOMID is

administered to patients with severe renal impairment. ZOLOMID 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.

Effect of Other Drugs on Temozolomide Pharmacokinetics: In a multiple-dose study, administration of ZOLOMID Capsules with ranitidine did not change the Cmax or AUC values for temozolomide or MTIC.

A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5%.

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

WARNING AND PRECAUTIONS

Myelosuppression

Patients treated with ZOLOMID 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 x 109 /L and a platelet count greater than or equal to 100 x 109 /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 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 ZOLOMID 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.

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 x 109 /L and the platelet count falls below 100 x 109 /L.

Hepatotoxicity

Fatal and severe hepatotoxicity have been reported in patients receiving ZOLOMID. 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 ZOLOMID.

Opportunistic infections and reactivation of infections

Opportunistic infections (such as Pneumocystis jirovecii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ

Hepatitis B virus

Hepatitis due to hepatitis B virus (HBV) reactivation, in some cases resulting in death, has been reported. Experts in liver disease should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease). During treatment patients should be monitored and managed appropriately.

Meningoencephalitis herpetic

In post-marketing cases, meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very rarely.

Anti-emetic therapy

Nausea and vomiting are very commonly associated with TMZ.

Anti-emetic therapy may be administered prior to or following administration of TMZ.

Adult patients with newly-diagnosed glioblastoma multiforme

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

Patients with recurrent or progressive malignant glioma

Patients who have experienced severe (Grade 3 or 4) vomiting in previous treatment cycles may require anti-emetic therapy.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving TMZ.

Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m^2 TMZ, teratogenicity and/or foetal toxicity were demonstrated. Temozolomide should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

Breast-feeding

It is not known whether TMZ is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with TMZ.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with TMZ.

SIDE EFFFECTS

The following adverse reactions have been identified during postapproval use of ZOLOMID. 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 ZOLOMID and, in some cases, recurred upon rechallenge.

Hematopoietic disorders: Prolonged pancytopenia, which may result in aplastic anemia and fatal outcomes.

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), 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

DRUG INTERACTIONS

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

In a separate phase I study, administration of TMZ 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 TMZ with food resulted in a 33 % decrease in C_{max} and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in C_{max} 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, H_2 receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of TMZ.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other medicinal products. However, since TMZ 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 TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

CONTRAINDICATIONS

ZOLOMID (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).

ZOLOMID 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).

Severe myelosuppression.

OVER DOSAGE

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.

STORAGE & INSTRUCTIONS

Store between 20-25°C.

Protect from heat, sunlight and moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Zolomid Capsule 100mg

5 capsules.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۲۵-۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے محفوظ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند اکولوجسٹ یا کینسر ہسپتال کے نسخہ پر فروخت کریں۔

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PHARMASOL
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Lahore, Pakistan.