Temonix

Temozolomide

COMPOSITION

Temonix 100 Capsule: Each capsule contains Temozolomide USP 100 mg.
Temonix 250 Capsule: Each capsule contains Temozolomide USP 250 mg.

CLINICAL PHARMACOLOGY

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 1-2.25 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/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.

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/m^2 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/m^2). Caution should be exercised when Temozolomide is administered to patients with severe renal impairment. 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.

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%.
A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered Temozolomide.

MECHANISM OF ACTION

Temozolomide is not directly active but undergoes rapid nonenzymatic 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 O^6 and N^7 positions of guanine.

INDICATIONS

Newly Diagnosed Glioblastoma Multiforme

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

Refractory Anaplastic Astrocytoma

Temonix 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

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

Refractory Anaplastic Astrocytoma: Initial dose 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D.

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 Temonix.

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 the drug to the mother from Temonix.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Renal Impairment

Caution should be exercised when Temonix is administered to patients with severe renal impairment.

Hepatic Impairment

Caution should be exercised when Temonix is administered to patients with severe hepatic impairment.

OVERDOSAGE

Doses of 500, 750, 1000, and 1250 mg/m^2 (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.

CONTRAINDICATIONS

Temonix is contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide MTIC).

PRECAUSIONS

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.
Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed.
Pneumocystis carinii pneumonia (PCP) - prophylaxis required for all patients receiving concomitant Temonix and radiotherapy for the 42-day regimen for the treatment of newly diagnosed glioblastoma multiforme.
All patients, particularly those receiving steroids, should be observed closely for the development of lymphopenia and PCP.
Complete blood counts should be obtained throughout the treatment course as specified.
Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving Temonix.

ADVERSE EFFECTS

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.
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. Allergic reactions have also been reported.

DRUG INTERACTIONS

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

PHARMACEUTICAL INFORMATION

Storage condition

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Temonix 100 Capsule: Each commercial box contains 6 Capsules in Alu-Alu blister pack.
Temonix 250 Capsule: Each commercial box contains 4 Capsules in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

LF13601