Relimide™

RELIC
Biotechnology Pvt. Ltd.
An ISO 9001:2008 Certified Company

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

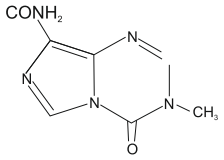
RELIMIDE™ Temozolomide Capsules I.P.

Composition

RELIMIDE -250
Each Capsule contains:
Temozolomide I.P. 250 mg.

RELIMIDE -100
Each Capsule contains
Temozolomide I.P. 100 mg.

RELIMIDE -20
Each Capsule contains
Temozolomide I.P. 20 mg.



Description :
RELIMIDE Capsules for oral administration contain temozolomide, an Imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxolmidazo[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 RELIMIDE can be administered orally. The prodrug, temozolomide is rapidly hydrolysed to the active 5-(3-methyltriazen-1-y1) 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 is not directly active but undergoes 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 mainly at the O_6 and O_7 positions of guanien.
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 0.4 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, 3-methyl-(triazen-1-y1) imidazole-4-car-boxamide (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 methythydrazine, 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. 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 as 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
Special Populations
Age Population pharmacokinetic analysis indicated that age (range 19 to 78 years) has no influence on the pharmacokinetic of temozolomide. 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 in the first cycle of therapy than patients under 70 years of age (see PRECAUTIONS). Gender Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidence of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men (see ADVERSE REACTIONS).
Race The effect of race on the pharmacokinetics of temozolomide has not been studied.
Tobacco Use Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.
Creatinine Clearance Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 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<36mL/min/m^2). Caution should be exercised when RELIMIDE Capsules are administered to patients with severe renal impairment. RELIMIDE has not been studied in patients on dialysis.

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 RELIMIDE 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, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Indications
RELIMIDE (Temozolomide) Capsules are indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.
RELIMIDE 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 RELIMIDE 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 : RELIMIDE is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance RELIMIDE 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 RELIMIDE 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 10^2/L platelet count> 100X10^2/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 RELIMIDE + RT PHASE, RELIMIDE 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 is escalated to 200 mg/m^2, 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 x10^2/L, and the platelet count is >100x10^2/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.
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

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 10^9/L	See footnote b
Platelet Count	<50x10^9/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b.]
a: TMZ dose level are listed in 6.		
b: TMZ is to be discontinued if dose reduction to <100 mg/m^2 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.		

For adults the initial dose is 150 mg/m^2 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 cycle) ANC are > 1.5x10^9/L (1,500/uL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are> 100x10^9/L (1,00,000/uL), the RELIMIDE 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 1.5x10^9/L (50,000/uL) 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. RELIMIDE 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

RELIMIDE 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 RELIMIDE

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 RELIMIDE , they should be advised to take these medications 30 minutes before they take RELIMIDE . 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 RELIMIDE capsules should be swallowed whole and **NEVER CHEWED.**

Adverse Reactions

Newly Diagnosed Glioblastoma Multiforme

During the concomitant phase (RELIMIDE + radiotherapy), adverse events including Thrombocytopenia, nausea, vomiting, anorexia and constipation, were more frequent in the RELIMIDE + 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 RELIMIDE experience were alopecia, nausea, vomiting, anorexia, headache, and constipation. Forty-nine percent (49%) of patients treated with RELIMIDE 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 RELIMIDE .

Drug Interactions

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

WARNING:

Patients treated with RELIMIDE Capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) > 1.5x10^9/L and Platelet count >100x10^9/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 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 **RELIMIDE** 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 RELIMIDE Capsules.

Precautions:

Patients with Severe Hepatic or Renal Impairment : Caution should be exercised when RELIMIDE 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 10^9/L and the platelet count falls below 100x10^9/L.

Carcinogenesis, Mutagenesis, and impairment of Fertility.

Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200mg /m^2 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/m^2 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 **RELIMIDE** Capsules, patients receiving RELIMIDE should discontinue nursing.

PEDIATRIC USE

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

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 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

RELIMIDE (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.

Presentation :

Each bottle of **RELIMIDE™ -250** contains 5 capsules.
Each bottle of **RELIMIDE™ -100** contains 5 capsules
Each bottle of **RELIMIDE™ - 20** contains 5 capsules

Storage:

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

RELIMIDE™