KEMTAX
Temozolomide 5 mg - 20 mg - 100 mg - 140 mg - 180 mg - 250 mg
Hard Capsules
Made in Argentina Under prescription only

Qualitative Formula
Each Kemtax capsule contains:
Active Ingredient: Temozolomide
Excipients: Anhydrous lactose, Sodium starch glycolate, Colloidal silicon dioxide, Tartaric acid, Stearic acid.

THERAPEUTIC ACTION
Imidazotetrazine alkylating agent with antitumor activity.

INDICATIONS
Temozolomide is indicated for the treatment of patients with:
• Newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as adjuvant therapy.
• Malignant glioblastoma, such as glioblastoma multiforme or anaplastic astrocytoma, that have progressed or recurred following conventional therapy.

PHARMACOLOGICAL CHARACTERISTICS/PROPERTIES
Pharmacological Action
At physiological pH, temozolomide undergoes rapid chemical conversion in the systemic circulation, transforming into the active compound MTIC (monomethyl triazene imidazole carboxamide). The cytotoxicity of MTIC is believed to be primarily due to guanine alkylation at the O^6 position, with additional alkylation occurring at the N^7 position. It is thought that subsequent cytotoxic lesions involve aberrant repair of the methyl adduct.
Pharmacokinetics
Preclinical data suggest that temozolomide rapidly crosses the blood-brain barrier and is present in the cerebrospinal fluid. After oral administration to adult patients, temozolomide is rapidly absorbed, reaching peak concentrations 20 minutes after the dose (average time between 0.5 and 1.5 hours). Plasma concentration increases are dose-related. Plasma clearance, volume of distribution, and half-life are independent of the dose.
Temozolomide has demonstrated low binding to plasma proteins (10% to 20%), therefore, no interaction is expected with agents that bind highly to them. After oral administration of ^{14}C-temozolomide, the average fecal excretion of ^{14}C over the 7 days following dosing reached 0.8%, indicating complete absorption. Following oral administration, 5% to 10% of the dose was recovered unchanged in the 24-hour urine, and the rest was excreted as AIC (4-amino-5-imidazole-carboxamide hydrochloride) or unidentified polar metabolites. Population-based analysis using pharmacokinetic data obtained with temozolomide revealed that drug plasma clearance was independent of age, renal function, hepatic function, or tobacco consumption.
Pediatric patients had a higher area under the curve compared to adult patients; however, the maximum tolerated dose was 1000 mg/m² per cycle for both children and adults.

DOSE/DOSAGE - MODE OF ADMINISTRATION
Adult patients with newly diagnosed glioblastoma multiforme
- Concomitant Phase
Temozolomide is administered orally at a dose of 75 mg/m², once daily, for 42 days, concomitantly with focal radiotherapy (60 Gy delivered in 30 sessions), followed by 6 cycles of temozolomide as adjuvant therapy. Dose reductions are not recommended; however, interruptions in medication may occur based on patient tolerance. Once the 42-day period of concomitant treatment is completed, the temozolomide dose may continue for up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, non-hematologic toxicity according to Common Toxicity Criteria (CTC) ≤ Grade 1 (except for alopecia, nausea, and vomiting). A complete blood count should be obtained weekly during treatment. The administration of temozolomide should be interrupted or discontinued during the concomitant phase according to the hematologic and non-hematologic toxicity criteria mentioned in Table 1.

Table 1: Interruption or discontinuation of Temozolomide (TMZ) administration during the concomitant phase of Temozolomide and radiotherapy.

TMZ Interruption	*TMZ Interruption*[a]	*TMZ Discontinuation*
Absolute Neutrophil Count	≥ 0,5 y < 1,5 x 10^9/l	< 0,5 x 10^9/l
Platelet Count	≥ 10 y < 100 x 10^9/l	< 10 x 10^9/l
Non-hematologic toxicity according to CTC (excluding alopecia, nausea, and vomiting)	CTC Grade 2	CTC Grade 3 o 4

[a]In the adjuvant phase, TMZ treatment can be continued if all of the following conditions are met: absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, non-hematologic toxicity according to CTC ≤ Grade 1 (excluding alopecia, nausea, and vomiting).

-Adjuvant Phase
Four weeks after completing the Temozolomide + Radiotherapy phase, Temozolomide is administered for an additional 6 cycles as adjuvant treatment. The dose in Cycle 1 (adjuvant) is 150 mg/m² once daily for 5 days, followed by 23 days without treatment. At the start of Cycle 2, the dose is increased to 200 mg/m² if the CTC for non-hematologic toxicity in Cycle 1 is Grade ≤ 2 (excluding alopecia, nausea, and vomiting), the absolute neutrophil count is ≥1.5 x 10^9/L, and the platelet count is ≥100 x 10^9/L. If the dose was not increased in Cycle 2, it should not be increased in subsequent cycles. The dosage is maintained at 200 mg/m² per day for the first 5 days of each subsequent cycle, unless toxicity is observed. Dose reductions during the adjuvant phase should be applied according to Tables 2 and 3. A complete blood count should be obtained on Day 22 (21 days after the first dose of Temozolomide) during treatment. The dose of Temozolomide should be reduced or discontinued according to Table 3.

Table 2 - Temozolomide dosing levels during adjuvant treatment

Level Dose	*Dosing* (mg/m²/day)	*Notes*
-1	100	Reduction due to previous toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in the absence of toxicity

Table 3 - Dose reduction or discontinuation of Temozolomide during adjuvant treatment

Toxicity	*Reduce TMZ dose by one level*[a]	*Discontinue TMZ*
Absolute Neutrophil Count	<1,0 x 10^9/l	See Note b
Platelet Count	<50 x 10^9/l	See Note b
CTC non-hematologic toxicity (excluding alopecia, nausea, and vomiting)	CTC Grade 3	CTC Grade 4[b]

[a]: TMZ dosing levels are indicated in Table 2.
[b]: TMZ should be discontinued if dose reduction to <100 mg/m² is required or if the same non-hematologic toxicity Grade 3 (excluding alopecia, nausea, vomiting) reappears after dose reduction.
TMZ = Temozolomide; CTC = Common Toxicity Criteria.

Adult patients with progressive or recurrent glioma
In previously untreated patients with no prior chemotherapy, Temozolomide is administered orally at a dose of 200 mg/m² once daily for 5 days, in 28-day cycles. In patients previously treated with chemotherapy, the initial dose is 150 mg/m2 once daily, which should be increased to 200 mg/m² in the second cycle, provided that the absolute neutrophil count is ≥1.5 x 10^9/l and the platelet count is ≥100 x 10^9/l on day 1 of the next cycle. Dose modification of Temozolomide should be based on toxicity, using the lowest values of absolute neutrophil count or platelet count as reference.

Pediatric patients with progressive or recurrent glioma
In patients aged 3 years and older, Temozolomide is administered orally at a dose of 200 mg/m² once daily for 5 days, in 28-day cycles. Pediatric patients previously treated with chemotherapy should receive an initial dose of 150 mg/m² once daily for 5 days, which should be increased to 200 mg/m² once daily for five days in the next cycle if no toxicity occurs. Treatment can be continued until disease progression, for a maximum of two years.

Laboratory parameters for dose modification in progressive or recurrent malignant glioma
Prior to dose administration, the following laboratory parameters must be met: absolute neutrophil count ≥1.5 x 10^9/l and platelet count ≥100 x 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 date, and weekly until the absolute neutrophil count is above 1.5 x 10^9/l and the platelet count exceeds 100 x 10^9/l. If during any cycle the neutrophil count falls to <1.0 x 10^9/l, or the platelet count is <50 x 10^9/l, the dose should be reduced by one level in the next cycle. Dose levels include 100 mg/m², 150 mg/m², and 200 mg/m². The lowest recommended dose is 100 mg/m².

Administration method
Temozolomide should be administered on an empty stomach, at least one hour before a meal. Antiemetic therapy may be administered before or after Temozolomide administration. If vomiting occurs after the dose is administered, a second dose should not be given on the same day.

CONTRAINDICATIONS
Temozolomide is contraindicated in patients with a history of hypersensitivity reactions to any of its components or to dacarbazine (DTIC). Temozolomide is contraindicated during pregnancy. Temozolomide is contraindicated in patients with severe myelosuppression.

WARNINGS
Patients receiving concomitant treatment with temozolomide and radiation therapy in a pilot trial conducted for the extended 42-day dosing regimen demonstrated a particular risk of developing Pneumocystis carinii pneumonia. Therefore, prophylaxis against Pneumocystis carinii is indicated in all patients receiving concomitant temozolomide and radiation therapy in a 42-day regimen (up to a maximum of 49 days). When temozolomide is administered during an extended dosing regimen, the occurrence of Pneumocystis carinii pneumonia may be higher. However, all patients treated with temozolomide, particularly those receiving steroids, should be closely monitored for the development of Pneumocystis carinii pneumonia, regardless of the regimen.
Anti-emetic therapy: Nausea and vomiting are commonly associated with the administration of temozolomide; the following guidelines are provided:

Patients with newly diagnosed glioblastoma multiforme:
- Anti-emetic prophylaxis is recommended prior to the initial dose of temozolomide administered concomitantly.
- Anti-emetic prophylaxis is strongly recommended during the adjuvant phase.
Patients with recurrent or progressive malignant glioma:
Patients experiencing severe vomiting (Grade 3 or 4) in previous treatment cycles may require anti-emetic therapy.

PRECAUTIONS
Drug interactions
The administration of temozolomide with ranitidine or with meals did not result in clinically significant alterations in drug absorption. Concurrent administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonist, or phenobarbital did not alter the clearance of temozolomide. Co-administration of valproic acid was associated with a small but statistically significant decrease in temozolomide clearance.
The use of temozolomide in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Use during pregnancy
There are no studies available in pregnant women. In preclinical trials conducted in rats and rabbits receiving 150 mg/m², teratogenicity and/or fetal toxicity were demonstrated. Therefore, temozolomide should not be normally administered during pregnancy. If the use of the drug needs to be considered during pregnancy, the patient should be informed of the potential risk to the fetus. Women of childbearing potential should be advised to avoid pregnancy while receiving temozolomide and for 6 months following discontinuation of the drug.

Use during lactation
It is unknown whether temozolomide is excreted in human milk; therefore, it should not be used during lactation.

Use in male patients
Male patients treated with Temozolomide should also use effective contraceptive methods. Temozolomide may have genotoxic effects. Therefore, men receiving Temozolomide should be advised not to impregnate their partner during treatment and for 6 months after treatment, and to seek advice on sperm cryopreservation before initiating therapy, due to the possibility of irreversible infertility as a result of Temozolomide use.

Use in Pediatrics
Glioblastoma multiforme: There is no clinical experience with the use of Temozolomide in children under 3 years of age. Clinical experience in children over 3 years with glioma is limited.

Use in Elderly Patients
Elderly patients (>70 years) appear to have a higher risk of developing neutropenia and thrombocytopenia compared to younger patients.

Use in Patients with Hepatic or Renal Impairment
The pharmacokinetics of Temozolomide were comparable in patients with normal hepatic function and those with mild to moderate hepatic dysfunction. There are no data available on the administration of Temozolomide to patients with severe hepatic impairment (Child-Pugh Class III) or renal dysfunction.
Based on the pharmacokinetic properties of the drug, dose reductions are unlikely to be required in patients with severe hepatic or renal impairment. However, caution is recommended when administering Temozolomide to these patients.

ADVERSE REACTIONS
Adult patients with newly diagnosed glioblastoma multiforme
Table 4 presents treatment-emergent adverse events (causality was not determined during clinical trials) in patients with newly diagnosed glioblastoma multiforme during the concurrent and adjuvant treatment phases.

Table 4 - Temozolomide and radiotherapy:
Treatment-emergent adverse events during the concurrent and adjuvant phases
Very common (≥1/10); Common (>1/100, <1/10); Rare (>1/1000, <1/100)

	TMZ + concomitant radiotherapy n=288*	TMZ monotherapy n=224
Infections and infestations		
Common:		Infection, oral candidiasis
Rare:	Oral candidiasis, herpes simplex, infection, pharyngitis, wound infection	Herpes simplex, herpes zoster, flu-like symptoms
Blood and lymphatic system disorders		
Common:	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anemia, leukopenia
Rare:	Febrile neutropenia, anemia	Lymphopenia, petechiae
Endocrine disorders		
Rare:	Cushingoid syndrome	Cushingoid syndrome
Metabolic and nutritional disorders		
Very common:	Anorexia	Anorexia
Common:	Hyperglycemia, weight loss	Weight loss
Rare:	Hypocalcemia, increased alkaline phosphatase, weight gain	Hyperglycemia, weight gain
Psychiatric disorders		
Common:	Anxiety, emotional lability, insomnia	Anxiety, depression, emotional lability, insomnia
Rare:	Agitation, apathy, behavioral changes, depression, hallucinations	Hallucinations, amnesia
Disorders of the nervous system		
Very common:	Headache	Seizures, headache
Common:	Seizures, decreased consciousness, drowsiness, aphasia, balance disorder, dizziness, confusion, memory loss, decreased concentration, neuropathy, paresthesia, speech disorder, tremor, drowsiness	Hemiparesis, aphasia, balance disorder, drowsiness, confusion, dizziness, memory loss, decreased concentration, dysphasia, unspecified neurological disorders, peripheral neuropathy, paresthesia, speech disorder, tremor
Rare:	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognitive disorder, dysphasia, gait disturbance, hyperesthesia, hypoesthesia, unspecified neurological disorders, peripheral neuropathy	Hemiplegia, ataxia, coordination disorder, gait disturbance, hyperesthesia, sensory disorder
Ocular disorders		
Common:	Blurred vision	Visual field defect, blurred vision, diplopia
Rare:	Hemianopsia, decreased visual acuity, visual impairment, visual field defect, eye pain	Decreased visual acuity, eye pain, dry eye
Auditory and balance disorders		
Common:	Hearing disorders	Hearing disorders, tinnitus
Rare:	Otitis media, tinnitus, hyperacusis, ear pain	Deafness, vertigo, ear pain
Cardiac disorders		
Rare:	Palpitations	
Vascular disorders		
Common:	Hemorrhage, edema, leg edema	Hemorrhage, deep vein thrombosis, leg edema
Rare:	Cerebral hemorrhage, hypertension	Pulmonary embolism, edema, peripheral edema
Respiratory, thoracic, and mediastinal disorders		
Common:	Dyspnea, cough	Dyspnea, cough
Rare:	Pneumonia, upper respiratory tract infection, nasal congestion	Pneumonia, sinusitis, upper respiratory tract infection, bronchitis
Gastrointestinal disorders		
Very Common:	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common:	Stomatitis, diarrhea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhea, dyspepsia, dysphagia, dry mouth
Rare:		Abdominal distension, fecal incontinence, unspecified gastrointestinal disorders, gastroenteritis, hemorrhoids

Skin and subcutaneous tissue disorders		
Very Common:	Skin rash, alopecia	Skin rash, alopecia
Common:	Dermatitis, dry skin, erythema, itching	Dry skin, itching
Rare:	Skin exfoliation, photosensitivity reaction, abnormal pigmentation	Erythema, abnormal pigmentation, increased sweating
Musculoskeletal and connective tissue disorders		
Common:	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia, muscle weakness
Rare:	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common:	Polyuria, urinary incontinence	Urinary incontinence
Rare:		Dysuria
Disorders of the reproductive system and breast		
Rare:	Impotence	Vaginal bleeding, menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very Common:	Fatigue	Fatigue
Common:	Allergic reaction, fever, radiation injury, facial edema, pain, taste alteration	Allergic reaction, fever, radiation injury, pain, taste alteration
Rare:	Flushing, hot flushes, asthenia, worsening of general condition, stiffness, discoloration of the tongue, parosmia, thirst	Asthenia, worsening of general condition, pain, stiffness, dental disorders, facial edema, taste alteration
Laboratory abnormalities		
Common:	Elevated GPT (liver enzyme)	Elevated GPT (liver enzyme)
Rare:	Elevated liver enzymes, elevated Gamma-GT, elevated GOAT (liver enzymes)	

*A patient randomized to the radiotherapy arm only received Temozolomide + radiotherapy.

Laboratory results: Myelosuppression (neutropenia and thrombocytopenia), a recognized dose-limiting toxicity for most cytotoxic agents, including Temozolomide, was observed. When laboratory abnormalities and adverse events were combined throughout the concomitant and adjuvant treatment phases, abnormalities in neutrophils Grade 3 or Grade 4, including neutropenic events, were observed in 8% of patients. Abnormalities in platelets Grade 3 or Grade 4, including thrombocytopenic events, were observed in 14% of patients who received Temozolomide.

Adverse events in patients with recurrent or progressive malignant glioma: In clinical trials, the most frequently reported adverse effects were gastrointestinal disorders, specifically nausea (43%) and vomiting (36%). These effects were usually Grade 1 or 2 (mild to moderate intensity) and resolved spontaneously or were easily controlled with standard antiemetic treatment. The incidence of severe nausea and vomiting was 4%. Other frequently reported adverse effects included fatigue (22%), constipation (17%), and headache (14%). Anorexia (11%), diarrhea (8%), rash, fever, asthenia, and drowsiness (6% each) were also reported. Less commonly (2% to 5%), and in decreasing order of frequency, abdominal pain, pain, dizziness, weight loss, discomfort, dyspnea, alopecia, chills, itching, dyspepsia, taste alteration, paresthesia, and petechiae were reported.

Laboratory results: Grade 3 or Grade 4 thrombocytopenia and neutropenia were observed in 19% and 17% respectively of patients treated for glioma. This led to hospitalization and/or discontinuation of temozolomide treatment in 8% and 4% of patients, respectively. Myelosuppression was predictable (usually occurring in the early cycles, reaching nadir between days 21 and 28), and recovery was rapid, typically within 1-2 weeks. There were no signs of cumulative myelosuppression. Pancytopenia, leukopenia, and anemia have also been reported. Lymphopenia was very commonly reported. Rare cases of opportunistic infections, including Pneumocystis carinii pneumonia, have been reported during the marketing of Temozolomide. Very rare cases of erythema multiforme and allergic reactions, including anaphylaxis, have been observed. Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been reported in patients treated with regimens containing Temozolomide. Very rare cases of prolonged pancytopenia, which can result in aplastic anemia, have been reported.

OVERDOSE

Clinically evaluated doses of 500, 750, 1000, and 1250 mg/m² (total dose per cycle over 5 days) have been evaluated in patients. Dose-limiting toxicity was hematological and was reported at any dose level, but is expected to be more severe at higher doses. One patient received an overdose of 2000 mg per day for 5 days and reported adverse effects including pancytopenia, fever, multiorgan failure, and death. There are reports of patients who have received treatment for more than 5 days (up to 64 days); reported adverse effects included bone marrow suppression, with or without infection, in some cases severe and prolonged, leading to death. In case of overdose, hematological evaluation is necessary. Implement general supportive measures as required.

In the event of an overdose, go to the nearest hospital or contact the toxicology centers:
- Hospital de Pediatria Dr. Ricardo Gutiérrez: (011) 4962-6666/2247
- Hospital Dr. A. Posadas: (011) 4654-6648/4658-7777

PRESENTATION

Packages containing 5 and 21 hard capsules.

STORAGE CONDITIONS

Store at a temperature below 30°C in its original packaging.

KEEP MEDICINES OUT OF THE REACH OF CHILDREN.
CONSULT YOUR DOCTOR IF YOU HAVE ANY DOUBTS.
Medication administered only under prescription and medical supervision.

MEDICINAL SPECIALTY AUTHORIZED BY THE MINISTRY OF HEALTH.
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