TemoRel Leaflet - Malaysia

Size: 100 mm x 380 mm

Colors:
Pantone Black C

Front Side

PACKAGE INSERT FOR

TemoRel Hard Capsules

20MG, 100MG AND 250MG

Product Name
TemoRel Hard Capsule 20mg
TemoRel Hard Capsule 100mg
TemoRel Hard Capsule 250mg

Name and Strength of Active Substance(s)
Each hard capsule contains:
Temozolomide 100mg
Temozolomide 250mg

Product Description
TemoRel Hard Capsule 20mg:
Size "2" hard gelatin capsule with yellow colored opaque cap and white colored opaque body, black colored printing text "TEMOZOLOMIDE" on cap and "20 mg" on body having off white to light pink colour powder inside the capsule.

TemoRel Hard Capsule 100mg:
Size "1" hard gelatin capsule with pink colored opaque cap and white colored opaque body, black colored printing text "TEMOZOLOMIDE" on cap and "100 mg" on body having off white to light pink coloured powder inside the capsule.

TemoRel Hard Capsule 250mg:
Size "0" hard gelatin capsule with white colored opaque cap and white colored opaque body, black colored printing text "TEMOZOLOMIDE" on cap and "250 mg" on body having off white to light pink coloured powder inside the capsule.

Pharmacodynamics
Antineoplastic agents - Other alkylating agents
Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Pharmacokinetics
Temozolomide (TMZ) is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O6 and N7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. In vivo, the t1/2 of MTIC was similar to that of TMZ, 1.8 hr.

Absorption
After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of 14C-labelled TMZ, mean faecal excretion of 14C over 7 days post-dose was 0.8 % indicating complete absorption.

Distribution
TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.
TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma.

Elimination
The half-life (t1/2) in plasma is approximately 1.8 hours. The major route of 14C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.
Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

Special populations
Plasma TMZ clearance is independent of age, renal function or tobacco use. Plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.
Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m^2 per cycle both in children and in adults.

Indication
TemoRel are indicated for the treatment of patients with:
- Newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as adjuvant treatment.
- Malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Dosage and Administration:
Adult patients with newly diagnosed glioblastoma multiforme:
Concomitant phase
TemoRel is administered orally at 75 mg/m2 daily for 42 days concomitant with radiotherapy (60 Gy administered in 30 fractions) followed by adjuvant TemoRel for 6 cycles.No dose reductions are recommended; however, dose interruptions may occur based on patient tolerance. The TemoRel dose can be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x109 /L thrombocyte count ≥ 100 x 109 /L common toxicity criteria (CTC) non-hematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. TemoRel dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in Table 1.

Table 1 TemoRel Dosing Interruption or Discontinuation during Concomitant Radiotherapy and TemoRel

Toxicity	TMZ Interruption [a]	TMZ Discontinuation
Absolute Neutrophil Count	≥ 0.5 and <1.5 x 10^9 /L	< 0.5 x 109 /L
Thrombocyte Count	≥ 10 and <100 x 10^9 /L	< 10 x 109 /L
CTC Non-hematological Toxicity(except for alopecia,nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant TMZ could be continued when all of the following conditions were 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).
TMZ = TemoRel; CTC = Common Toxicity Criteria

Adjuvant Phase
Four weeks after completing the TemoRel +Radiotherapy phase, TemoRel is administered for an additional 6 cycles of adjuvant treatment. Dosage in Cycle 1 (adjuvant) 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-hematologic 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. 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 during the adjuvant 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 TemoRel). The TemoRel dose should be reduced or discontinued according to Table 3.

Table 2 TemoRel Dose Levels for Adjuvant 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 TemoRel Dose Reduction or Discontinuation during Adjuvant Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinuation 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-hematological 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 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 = TemoRel ; CTC = Common Toxicity Criteria.

Adults with recurrent or progressive glioma: In patients previously untreated with chemotherapy, TemoRel is administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. 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 daily providing the absolute neutrophil count (ANC) is ≥ 1.5 x 10^9 /L and the thrombocyte count is ≥ 100 x 10^9/L on Day 1 of the next cycle. Dose modification for TemoRel should be based on toxicities according to nadir ANC or platelet counts.

Pediatric patient with recurrent or progressive glioma: In patients 3 years of age or older, TemoRel is administered orally at a dose of 200 mg/m^2 once daily for 5 days per 28-day cycle. Pediatric patients previously treated with chemotherapy should receive an initial dose of 150 mg/m^2 once daily for 5 days, with escalation to 200 mg/m^2 once daily for 5 days at the next cycle if there is no toxicity.
Therapy can be continued until disease progression for a maximum of 2 years.

All Patients:
TemoRel should be administered in the fasting state, at least one hour before a meal. Antiemetic therapy may be administered prior to or following administration of TemoRel. If vomiting occurs after the dose is administered, a second dose should not be administered that day.
TemoRel must not be opened or chewed, but are to be swallowed whole with a glass of water. If a capsule becomes damaged, avoid contact of the powder contents with skin or mucous membrane.

Route of Administration
Oral

Contraindications
Hypersensitivity to the active substance or to any of the excipients list
Hypersensitivity to dacarbazine (DTIC).
Severe myelosuppression.

Warnings and Precautions
Opportunistic infections and reactivation of infections
Opportunistic infections (such as Pneumocystis carinii pneumonia) and reactivation of infections (such as HBV, CMV) have been observed during the treatment with TMZ (see section Adverse Effects/ Undesirable Effects).

Meningoencephalitis herpetic
Meningoencephalitis herpetic (including fatal cases) has been observed in patients receiving TMZ in combination with radiotherapy, including cases of concomitant steroids administration.

Pneumocystis carinii pneumonia
Patients who received concomitant TMZ and radiotherapy (RT) for the prolonged 42-day schedule were shown to be at particular risk for developing Pneumocystis carinii pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant TMZ and RT for the 42-day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphopenia occurs, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1.
There may be a higher occurrence of PCP when TMZ is administered during a longer dosing regimen. However, all patients receiving TMZ, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using TMZ, in particular in combination with dexamethasone or other steroids.

HBV
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.

Hepatotoxicity
Hepatic injury, including fatal hepatic failure, has been reported in patients receiving temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risks prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle, liver function test should be repeated midway during this cycle. For all patients, liver function tests should be checked after treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/ risks of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

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.

Laboratory parameters
Patients treated with TMZ may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anaemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anaemia, including carbamazepine, phenytoin, and sulfamethoxazole / trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC ≥ 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 day, and weekly until ANC > 1.5 x 10^9/l and platelet count > 100 x 10^9/l. If ANC falls to < 1.0 x 10^9/l or the platelet count is < 50 x 10^9/l during any cycle, the next cycle should be reduced one dose level (see section 4.2). Dose levels include 100 mg/m^2, 150 mg/m^2, and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

Paediatric population
There is no clinical experience with use of TMZ in children under the age of 3 years. Experience in older children and adolescents is very limited.

Elderly patients (> 70 years of age)
Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when TMZ is administered in elderly patients

Male patients
Men being treated with TMZ 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.

Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interactions with Other Medicaments
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 Cmax and a 9 % decrease in area under the curve (AUC).
As it cannot be excluded that the change in Cmax is clinically significant, Temozolomide should be administered without food.
Co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H2 receptor antagonists, or phenobarbital did not alter the clearance of TMZ. Coadministration 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.

Paediatric population
No interaction studies have been performed in paediatric population.

Statement on usage during pregnancy and lactation
Pregnancy: Category D
There are no data in pregnant women.Temozolomide should not be administered to pregnant women. If use during pregnancy must be considerd, 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.

Women of childbearing potential
Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.

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.

Adverse Effects/ Undesirable Effects
Tabulated list of adverse reactions

Table 4. Adverse reactions in patients treated with temozolomide

Infections and infestations	
Common:	Infections, herpes zoster, pharyngitis[a], candidiasis oral
Uncommon:	Opportunistic infection (including PCP), sepsis[f], meningoencephalitis herpetic[f], CMV infection, CMV reactivation, hepatitis B virus[f], herpes simplex, infection reactivation, wound infection, gastroenteritis[b]
Neoplasm benign, malignant, and unspecified	
Uncommon:	Myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Blood and lymphatic system disorder	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia[f], pancytopenia, petechiae
Immune system disorders	
Common:	Allergic reaction
Uncommon:	Anaphylaxis
Endocrine disorders	
Common:	Cushingoid[c]
Uncommon:	Diabetes insipidus
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hyperglycaemia
Uncommon:	Hypokalaemia, alkaline phosphatase increase
Psychiatric disorders	
Common:	Agitation, amnesia, depression, anxiety, confusion, insomnia
Uncommon:	Behaviour disorder, emotional lability, hallucination, apathy
Nervous system disorders	
Very common:	Convulsions, hemiparesis, aphasia/dysphasia, headache
Common:	Ataxia, balance impaired, cognition impaired, concentration impaired, consciousness decreased, dizziness, hypoesthesia, memory impaired, neurologic disorder, neuropathy[d], paraesthesia, somnolence, speech disorder, taste perversion, tremor
Uncommon:	Status epilepticus, hemiplegia, extrapyramidal disorder, parosmia, gait abnormality, hyperaesthesia, sensory disturbance, coordination abnormal
Eye disorders	
Common:	Hemianopia, vision blurred, vision disorder[e], visual field defect, diplopia, eye pain
Uncommon:	Visual acuity reduced, eyes dry
Ear and labyrinth disorders	
Common:	Deafness[f], vertigo, tinnitus, earache[g]
Uncommon:	Hearing impairment, hyperacusis, otitis media
Cardiac disorders	
Uncommon:	Palpitation
Vascular disorders	
Common:	Haemorrhage, embolism pulmonary, deep vein thrombosis, hypertension
Uncommon:	Cerebral haemorrhage, flushing, hot flushes
Respiratory, thoracic and mediastinal disorders	
Common:	Pneumonia, dyspnoea, sinusitis, bronchitis, coughing, upper respiratory infection
Uncommon:	Respiratory failure[f], interstitial pneumonitis/pneumonitis, pulmonary fibrosis, nasal congestion
Gastrointestinal disorders	
Very common:	Diarrhoea, constipation, nausea, vomiting
Common:	Stomatitis, abdominal pain[h], dyspepsia, dysphagia
Uncommon:	Abdominal distension, faecal incontinence, gastrointestinal disorder, haemorrhoids, mouth dry
Hepatobiliary disorders	
Uncommon:	Hepatic failure[f], hepatic injury, hepatitis, cholestasis, hyperbilirubinemia
Skin and subcutaneous tissue disorders	
Very common:	Rash, alopecia
Common:	Erythema, dry skin, pruritus
Uncommon:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, erythroderma, skin exfoliation, photosensitivity reaction, urticaria, exanthema, dermatitis, sweating increased, pigmentation abnormal
Not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	
Common:	Myopathy, muscle weakness, arthralgia, back pain, musculoskeletal pain, myalgia
Renal and urinary disorders	
Common:	Micturition frequency, urinary incontinence
Uncommon:	Dysuria
Reproductive system and breast disorders	
Uncommon:	Vaginal haemorrhage, menorrhagia, amenorrhoea, vaginitis, breast pain, impotence
General disorders and administration site conditions	
Very common:	Fatigue
Common:	Fever, influenza-like symptoms, asthenia, malaise, pain, oedema, oedema peripheral[i]
Uncommon:	Condition aggravated, rigors, face oedema, tongue discolouration, thirst, tooth disorder
Investigations	
Common:	Liver enzymes elevationj, weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Investigations	
Common:	Radiation injury[k]

[a] Includes pharyngitis, nasopharyngeal pharyngitis, pharyngitis Streptococcal
[b] Includes gastroenteritis, gastroenteritis viral
[c] Includes cushingoid, Cushing syndrome
[d] Includes neuropathy, peripheral neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral motor neuropathy
[e] Includes visual impairment, eye disorder
[f] Includes deafness, deafness bilateral, deafness neurosensory, deafness unilateral
[g] Includes earache, ear discomfort
[h] Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort
[i] Includes oedema peripheral, peripheral swelling
[j] Includes liver function test increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased
[k] Includes radiation injury, radiation skin injury
[f] Including cases with fatal outcome

Newly-diagnosed glioblastoma multiforme
Laboratory results
Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including TMZ, was observed. When laboratory abnormalities and adverse events were combined across concomitant and monotherapy treatment phases, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in patients who received TMZ.

Recurrent or progressive malignant glioma
Laboratory results
Grade 3 or 4 thrombocytopenia and neutropenia occurred in patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ. Myelosuppression was predictable (usually within the first few cycles, with the nadir between Day 21 and Day 28), and recovery was rapid, usually within 1-2 weeks. No evidence of cumulative myelosuppression was observed. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

Paediatric population
Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of TMZ in children under the age of 3 years has not been established.

Drive and ability to use machines:
Temozolomide may make you feel tired or sleepy. In this case, do not drive or use any tools or machines or cycle until you see how this medicine affects you.

Overdose and Treatment
Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

Storage Condition.
Do not store above 30°C.Keep the bottle tightly closed in order to protect from moisture.

Dosage forms and packaging available
The capsules for oral use are filled in amber glass bottles. Each bottle contains 5 capsules.

Nature and contents of container
Bottle presentation
Amber coloured USP Type III glass bottles with polypropylene child-resistant closures containing 5 hard capsules.
The carton contains one bottle.

Instruction for use
TemoRel hard capsules 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.

Special precautions for disposal and other handling
Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If TemoRel comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.
Patients should be advised to keep capsules out of the sight and reach of children, preferably in a lock upboard. Accidental ingestion can be lethal for children

Date of revision
18 April 2024

Product Registration Holder:
Mansa Healthcare Sdn Bhd,
B-05-3A, 3 Two Square,
No 2, Jalan 19/1, 46300 Petaling Jaya,
Selangor, Malaysia

Reliance Life Sciences
Manufactured by:
Reliance Life Sciences Pvt. Ltd.
Dhirubhai Ambani Life Science Centre (DALC)
Plant 6, R-2B2, TTC Area of MIDC,
Thane – Belapur Road, Rabale,
Navi Mumbai -400701, India

1200026735 V01