ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 5 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 168 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have a white coloured body, a green coloured cap, and are imprinted with black ink. The cap is imprinted with “TMZ”. The body is imprinted with “5”.

Each capsule is approximately 15.8 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/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 $> 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least 3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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..

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for at least3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic

adverse reactions were reported commonly; the frequency of grade 3-4 laboratory findings is presented after table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention:

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, herpes simplex, infection reactivation, wound infection, gastroenteritisb
Neoplasm benign, malignant, and unspecified	
Uncommon:	Myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Blood and lymphatic system disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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

† 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 in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is

expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

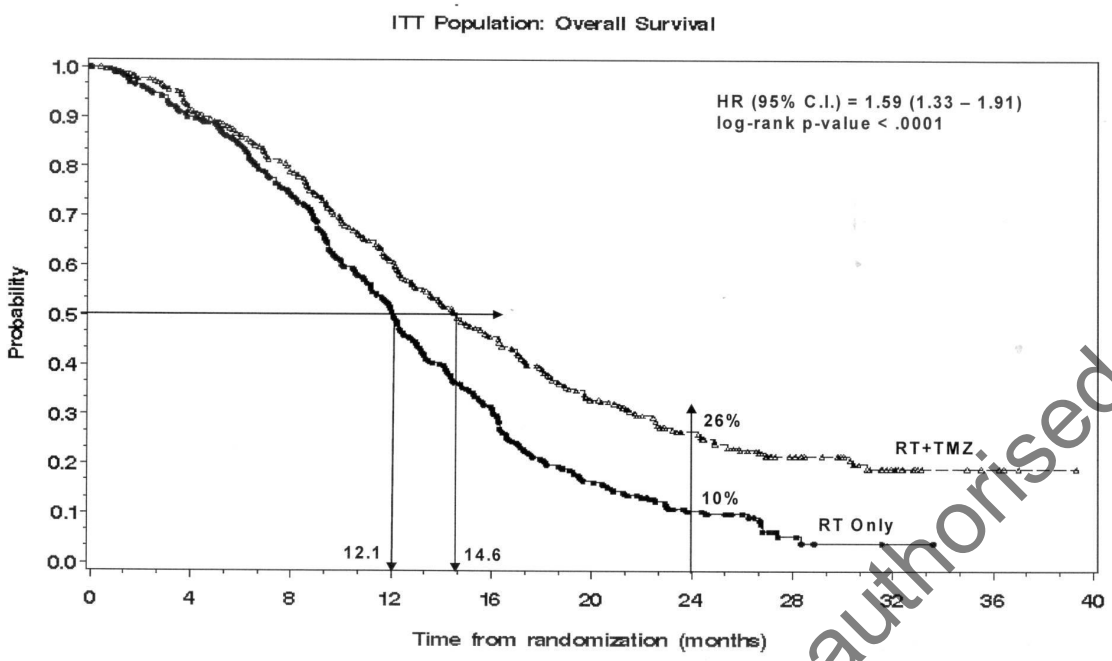

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the

central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Indigo carmine (E 132)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle
Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.
Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/001
EU/1/10/616/002
EU/1/10/616/025
EU/1/10/616/026
EU/1/10/616/037

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 14.6 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

The hard capsules have a white coloured body, a yellow coloured cap, and are imprinted with black ink. The cap is imprinted with “TMZ”. The body is imprinted with “20”.

Each capsule is approximately 11.4 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/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 $> 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least 3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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 .

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential haveto use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for a least 3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, herpes simplex, infection reactivation, wound infection, gastroenteritisb
Neoplasm benign, malignant, and unspecified	
Uncommon:	Myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Blood and lymphatic system disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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
[†] 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 in 8 % of the patients. Grade 3

or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

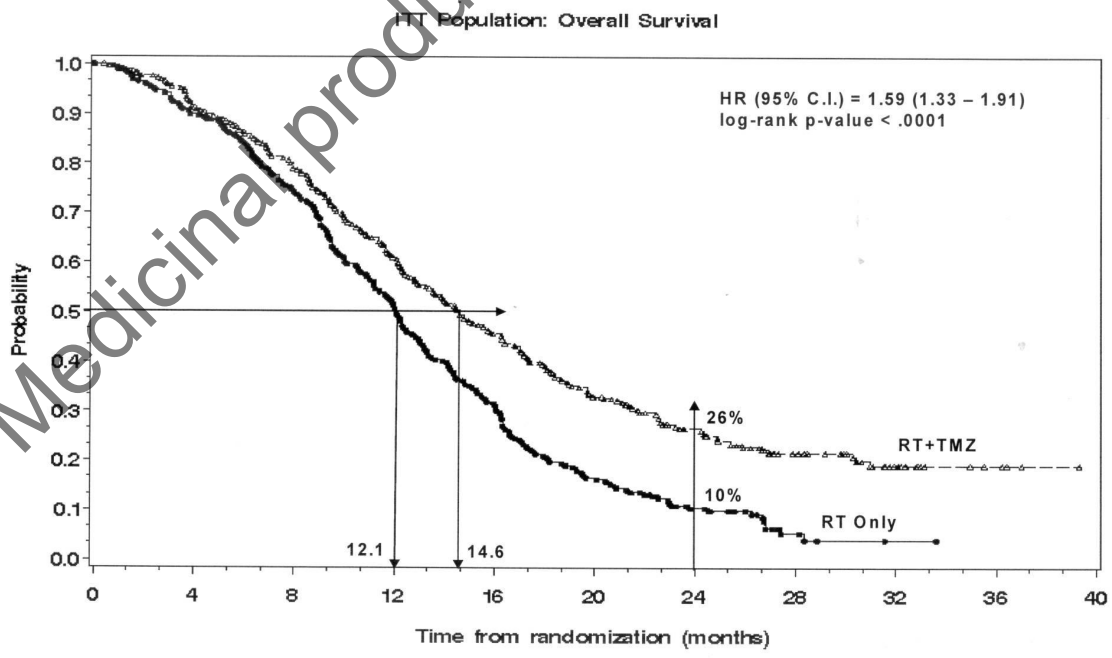

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle
Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.
Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/005
EU/1/10/616/006
EU/1/10/616/027
EU/1/10/616/028
EU/1/10/616/038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 73 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have a white coloured body, a pink coloured cap, and are imprinted with black ink. The cap is imprinted with “TMZ”. The body is imprinted with “100”.

Each capsule is approximately 15.8 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/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 $> 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least 3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for a least3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic

adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

.
For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, 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 disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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
[†] 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 in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

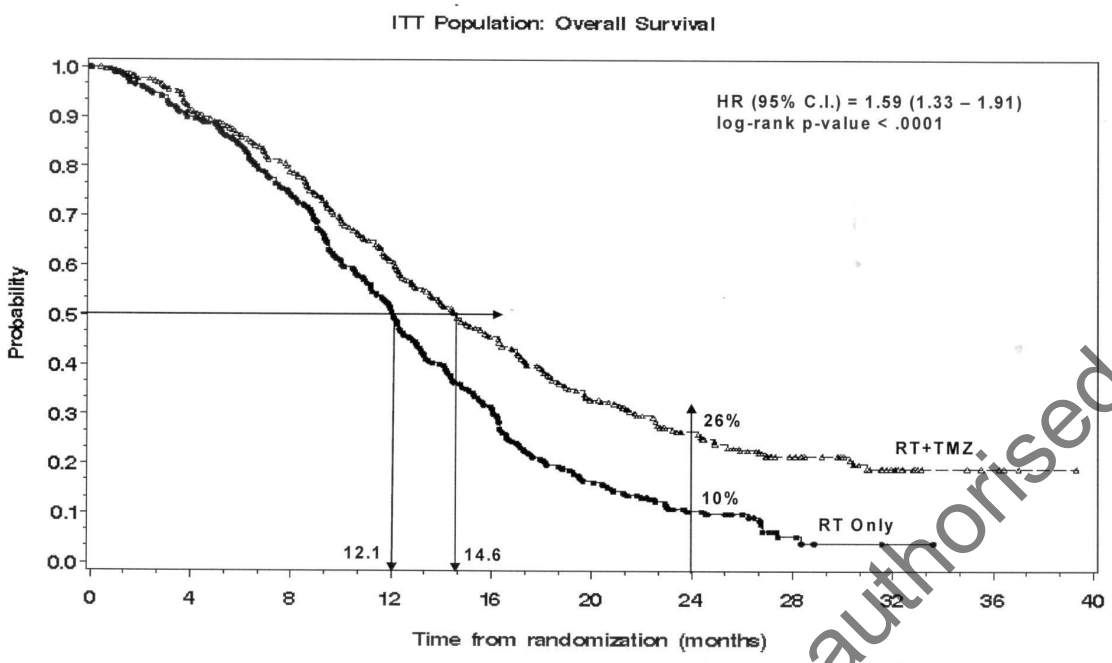

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the

central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.
PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Red iron oxide (E 172)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle

Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.
Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/009
EU/1/10/616/010
EU/1/10/616/029
EU/1/10/616/030
EU/1/10/616/039

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 140 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 140 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 102.2 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have a white coloured body, a transparent blue coloured cap, and are imprinted with black ink. The cap is imprinted with "TMZ". The body is imprinted with "140".

Each capsule is approximately 19.3 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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 duringconcomitant 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq$ 1.5 x 10^9/l and platelet count $\geq$ 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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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 .

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, , and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for at least3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic

adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, 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 disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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
[†] 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 in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In

the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

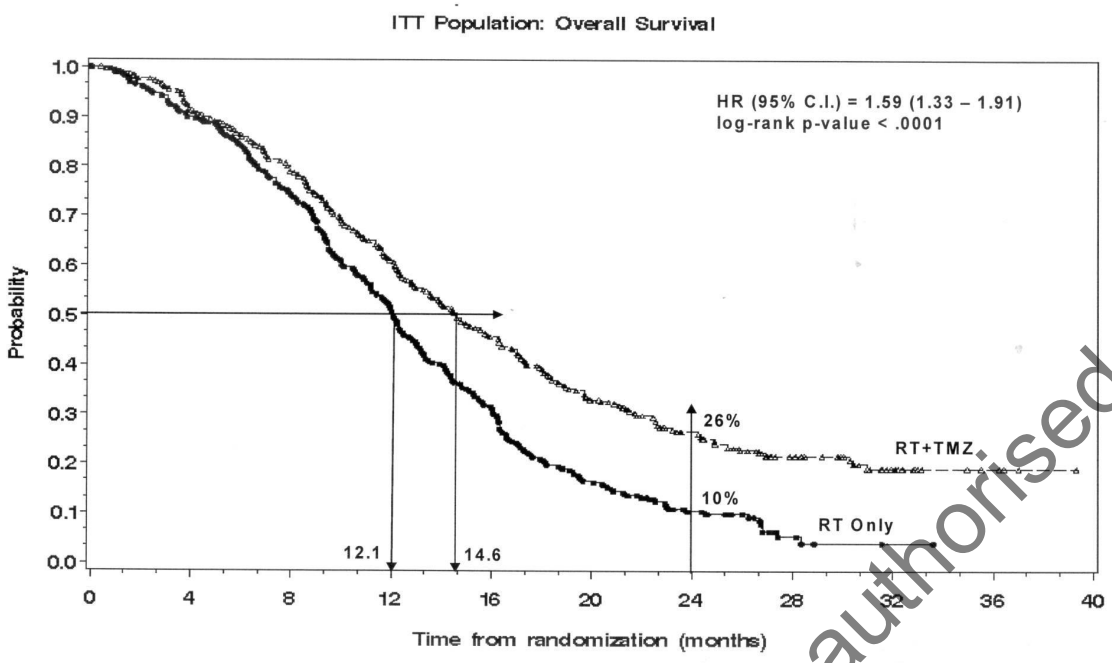

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the

central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.
PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Indigo carmine (E 132)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle

Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.
Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/013
EU/1/10/616/014
EU/1/10/616/031
EU/1/10/616/032
EU/1/10/616/040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 180 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 180 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 131.4 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have a white coloured body, a maroon coloured cap, and are imprinted with black ink. The cap is imprinted with "TMZ". The body is imprinted with "180".

Each capsule is approximately 19.3 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/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 $> 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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 .

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, , and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for at least 3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, 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 disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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
[†] Including cases with fatal outcome

Newly-diagnosed glioblastoma multiformeLaboratory 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 in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma
Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

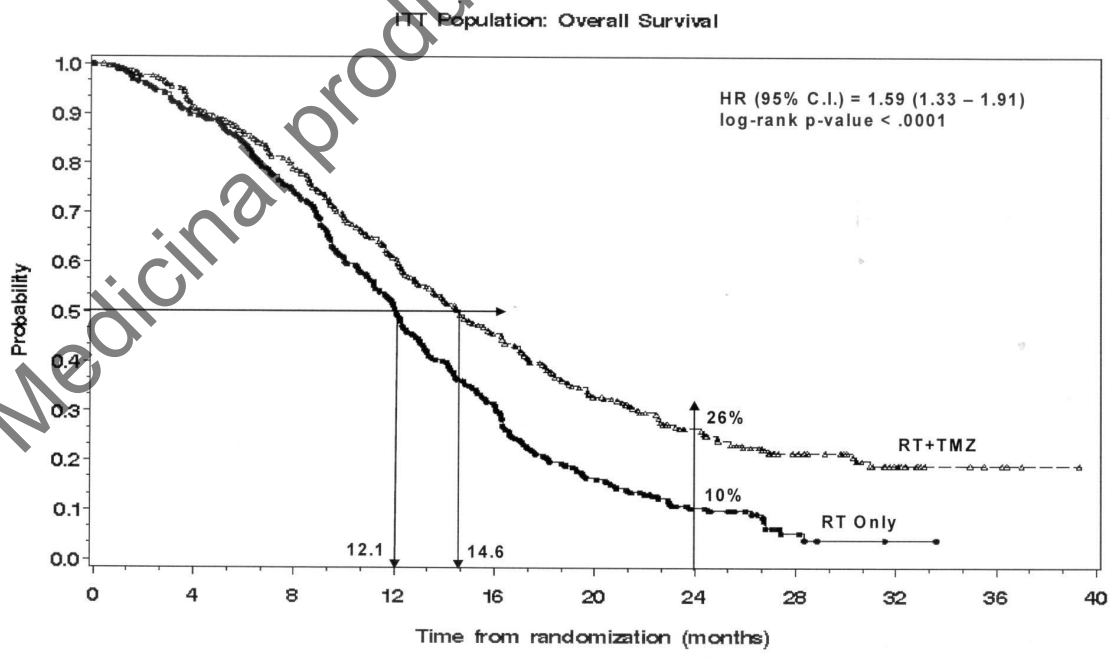

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid

Capsule shell:
Gelatin
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle
Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.
Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/017
EU/1/10/616/018
EU/1/10/616/033
EU/1/10/616/034
EU/1/10/616/041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg of temozolomide.

Excipient with known effect:
Each hard capsule contains 182.5 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The hard capsules have a white coloured body, a white coloured cap, and are imprinted with black ink. The cap is imprinted with "TMZ". The body is imprinted with "250".

Each capsule is approximately 21.4 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Temozolomide Hexal is indicated for the treatment of:
- adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

4.2 Posology and method of administration

Temozolomide Hexal should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered (see section 4.4).

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide Hexal 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-haematological 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-haematological 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[a]	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 (see section 4.4).

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 (see sections 4.4 and 5.1). 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 (see section 4.4).

Method of administration

Temozolomide Hexal 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression (see section 4.4).

4.4 Special warnings and precautions for use

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 (see section 4.8).

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.

Pneumocystis jirovecii pneumonia

Patients who received concomitant TMZ and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* 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 treated with TMZ (see section 4.8). Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities, physicians should assess the benefit/risk 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 (see section 4.8).

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 $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/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 $> 1.5 \times 10^9$/l and platelet count $> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/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 (see sections 4.2 and 5.1).

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.

Female patients

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male patients

Men being treated with TMZ should be advised not to father a child for at least 3 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment (see section 4.6).

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.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 Hexal 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 (see section 5.2).

Use of TMZ in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). Temozolomide Hexal 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.

Women of childbearing potential

Women of childbearing potential have to use effective contraception to avoid pregnancy while they are receiving TMZ, and for at least 6 months following completion of treatment.

Male fertility

TMZ can have genotoxic effects. Therefore, men being treated with it should use effective contraceptive measures and be advised not to father a child for at least3 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.

4.7 Effects on ability to drive and use machines

TMZ has minor influence on the ability to drive and use machines due to fatigue and somnolence (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Clinical trial experience

In patients treated with TMZ in clinical trials, the most common adverse reactions were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Most haematologic

adverse reactions were reported commonly; the frequency of Grade 3-4 laboratory findings is presented after Table 4.

For patients with recurrent or progressive glioma, nausea (43 %) and vomiting (36 %) were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies and reported from post-marketing use of TMZ are listed in Table 4. These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known: frequency cannot be estimated from the available data.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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†, meningoencephalitis herpetic†, CMV infection, CMV reactivation, hepatitis B virus†, 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 disorders	
Common:	Febrile neutropenia, neutropenia, thrombocytopenia, lymphopenia, leukopenia, anaemia
Uncommon:	Prolonged pancytopenia, aplastic anaemia†, 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 increased
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[†], 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[†], 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 elevation[j], weight decreased, weight increased
Uncommon:	Gamma-glutamyltransferase increased
Injury, poisoning and procedural complications	
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
[†] 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 in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received TMZ.

Recurrent or progressive malignant glioma

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of TMZ in 8 % and 4 %, respectively. 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.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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 haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 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 the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - Other alkylating agents, ATC code: L01AX03

Mechanism of action

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 O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either TMZ + RT (n=287) or RT alone (n=286). Patients in the TMZ + RT arm received concomitant TMZ (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy TMZ (150-200 mg/m^2) on Days 1-5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only. *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis was required during RT and combined TMZ therapy.

TMZ was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the TMZ + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33-1.91) with a log-rank $p < 0.0001$ in favour of the TMZ arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + TMZ arm. The addition of concomitant TMZ to RT, followed by TMZ monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

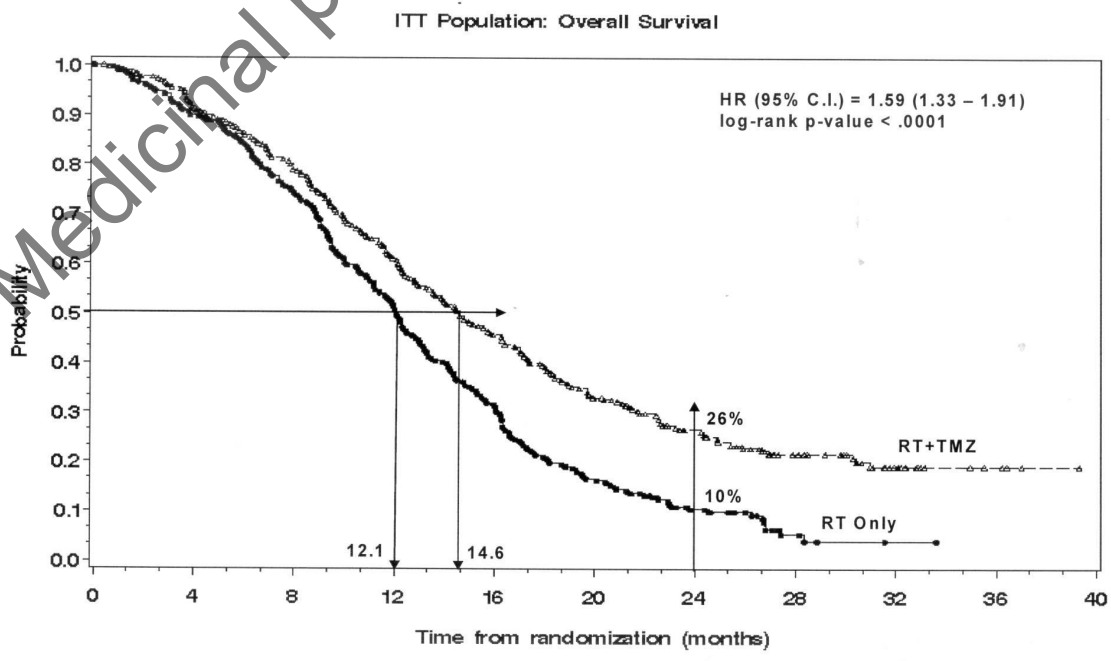

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

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 O^6 and N^7 positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ 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 ^{14}C-labelled TMZ, mean faecal excretion of ^{14}C 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.

PET studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C 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

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, 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.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Anhydrous lactose
Colloidal anhydrous silica
Sodium starch glycolate type A
Tartaric acid
Stearic acid
Capsule shell:
Gelatin
Titanium dioxide (E 171)
Water

Printing ink:
Shellac
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottle
Do not store above 25 °C.
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25 °C.

6.5 Nature and contents of container

Bottle
Type III amber glass bottle with polypropylene child-resistant closure containing 5 or 20 hard capsules.
The bottles contain a desiccant pouch.
The carton contains one bottle.

Multipack (Bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in a type III amber glass bottle with polypropylene child-resistant closure. The bottles contain a desiccant pouch.)

Sachet
Polyester/aluminium/polyethylene (PET/alu/PE) sachet.
Each sachet contains 1 hard capsule.

Pack-size of 5 or 20 hard capsules individually sealed in sachets.

Not all pack sizes may be marketed.

6.6 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 Temozolomid Hexal 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 locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/021
EU/1/10/616/022
EU/1/10/616/035
EU/1/10/616/036
EU/1/10/616/042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 19 November 2014

10. DATE OF REVISION OF THE TEXT

{ MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
D-39179 Barleben
Germany

Lek Pharmaceuticals d.d
Verovskova 57
SL-1526 Ljubljana
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON CONTAININGBOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 5 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 5 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/001
EU/1/10/616/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 20 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 20 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/005
EU/1/10/616/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}

SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 100 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 100 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/009
EU/1/10/616/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}

SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 140 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 140 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/013
EU/1/10/616/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}

SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 180 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 180 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/017
EU/1/10/616/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 250 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 250 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules
20 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/021
EU/1/10/616/022

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}

SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 5 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 5 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/037

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 20 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 20 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/038

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 100 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 100 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/039

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 140 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 140 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/040

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 180 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 180 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/041

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITH THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 250 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 250 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 20 (4 packs of 5) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/042

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}

NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 5 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 5 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/037 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 20 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/038 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 100 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 100 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/039 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 140 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 140 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/040 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 180 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 180 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/041 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR MULTIPACKS OF 20 (4 PACKS OF 5) HARD CAPSULES - WITHOUT THE BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 250 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 250 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/042 20 (4 packs of 5) hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 5 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 20 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 100 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 140 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 180 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 250 mg hard capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 hard capsules
20 hard capsules

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 5 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 5 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/025
EU/1/10/616/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 20 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 20 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/027
EU/1/10/616/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 100 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 100 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/029
EU/1/10/616/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 140 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 140 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/031
EU/1/10/616/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 140 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 180 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 180 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic.
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/033
EU/1/10/616/034

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 180 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SACHETS

1. NAME OF THE MEDICINAL PRODUCT

Temozolomide Hexal 250 mg hard capsules
temozolomide

2. STATEMENT OF ACTIVE SUBSTANCES

Each hard capsule contains 250 mg of temozolomide.

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

5 x 1 hard capsule in sachet
20 x 1 hard capsule in sachet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

7. OTHER SPECIAL WARNING, IF NECESSARY

Cytotoxic
Do not open, crush or chew the capsules, swallow whole. If a capsule is damaged, avoid contact with your skin, eyes or nose.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/616/035
EU/1/10/616/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Temozolomide Hexal 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 5 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 20 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 100 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 140 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 180 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Temozolomide Hexal 250 mg capsules
temozolomide

Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 capsule

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

Temozolomide Hexal 5 mg hard capsules

Temozolomide Hexal 20 mg hard capsules

Temozolomide Hexal 100 mg hard capsules

Temozolomide Hexal 140 mg hard capsules

Temozolomide Hexal 180 mg hard capsules

Temozolomide Hexal 250 mg hard capsules

temozolomide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Temozolomide Hexal is and what it is used for

Temozolomide Hexal contains a medicine called temozolomide. This medicine is an antitumour agent.

Temozolomide Hexal is used for the treatment of specific forms of brain tumours:
- in adults with newly-diagnosed glioblastoma multiforme. Temozolomide Hexal is first used together with radiotherapy (concomitant phase of treatment) and after that alone (monotherapy phase of treatment).
- in children 3 years and older and adult patients with malignant glioma , such as glioblastoma multiforme or anaplastic astrocytoma. Temozolomide Hexal is used in these tumours if they return or get worse after standard treatment.

2. What you need to know before you take Temozolomide Hexal

Do not take Temozolomide Hexal

- if you are allergic to temozolomide or any of the other ingredients of this medicine (listed in section 6).

- if you have had an allergic reaction to dacarbazine (an anticancer medicine sometimes called DTIC). Signs of allergic reaction include feeling itchy, breathlessness or wheezing, swelling of the face, lips, tongue or throat.
- if certain kinds of blood cells are severely reduced (myelosuppression), such as your white blood cell count and platelet count. These blood cells are important for fighting infection and for proper blood clotting. Your doctor will check your blood to make sure you have enough of these cells before you begin treatment.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Temozolomide Hexal

- as you should be observed closely for the development of a serious form of chest infection called *Pneumocystis jirovecii* pneumonia (PCP). If you are a newly-diagnosed patient (glioblastoma multiforme) you may be receiving Temozolomide Hexal for 42 days in combination with radiotherapy. In this case, your doctor will also prescribe medicine to help you prevent this type of pneumonia (PCP).
- if you have ever had or might now have a hepatitis B infection. This is because temozolomide could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.
- if you have low counts of red blood cells (anaemia), white blood cells and platelets, or blood clotting problems before starting the treatment, or if you develop them during treatment. Your doctor may decide to reduce the dose, interrupt, stop or change your treatment. You may also need other treatments. In some cases, it may be necessary to stop treatment with Temozolomide Hexal. Your blood will be tested frequently during treatment to monitor the side effects of Temozolomide Hexal on your blood cells.
- as you may have a small risk of other changes in blood cells, including leukaemia.
- if you have nausea (feeling sick in your stomach) and/or vomiting which are common side effects of Temozolomide Hexal (see section 4), your doctor may prescribe you a medicine (an anti-emetic) to help prevent vomiting.
  If you vomit frequently before or during treatment, ask your doctor about the best time to take Temozolomide Hexal until the vomiting is under control. If you vomit after taking your dose, do not take a second dose on the same day.
- if you develop fever or symptoms of an infection, contact your doctor immediately.
- if you are older than 70 years of age. You might be more prone to infections, bruising or bleeding.
- if you have liver or kidney problems. Your dose of Temozolomide Hexal may need to be adjusted.

Children and adolescents

Do not give this medicine to children under the age of 3 years because it has not been studied. There is limited information in patients over 3 years of age who have taken Temozolomide Hexal.

Other medicines and Temozolomide Hexal

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because you must not be treated with Temozolomide Hexal during pregnancy unless clearly indicated by your doctor.

Effective contraceptive precautions must be taken by **female patients** who are able to become pregnant dureing treatment with Temozolomide Hexal, and for at least 6 months months following completion of treatment.

You should stop breast-feeding while receiving treatment with Temozolomide Hexal.

Male fertility

Temozolomide Hexal may cause permanent infertility. Male patients should use effective contraception and not father a child for at least 3 months after stopping treatment. It is recommended to seek advice on conservation of sperm prior to treatment.

Driving and using machines

Temozolomide Hexal 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 (see section 4).

Temozolomide Hexal contains lactose and sodium

Temozolomide Hexal contains lactose (a kind of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

3. How to take Temozolomide Hexal

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Dosage and duration of treatment

Your doctor will work out your dose of Temozolomide Hexal. This is based on your size (height and weight) and if you have a recurrent tumour and have had chemotherapy treatment in the past.

You may be given other medicines (anti-emetics) to take before and/or after taking Temozolomide Hexal to prevent or control nausea and vomiting.

Patients with newly-diagnosed glioblastoma multiforme

If you are a newly-diagnosed patient, treatment will occur in two phases:
- treatment together with radiotherapy (concomitant phase) first
- followed by treatment with only Temozolomide Hexal (monotherapy phase).

During the concomitant phase, your doctor will start Temozolomide Hexal at a dose of 75 mg/m^2 (usual dose). You will take this dose every day for 42 days (up to 49 days) in combination with radiotherapy. The Temozolomide Hexal dose may be delayed or stopped, depending on your blood counts and how you tolerate your medicine during the concomitant phase.

Once the radiotherapy is completed, you will interrupt treatment for 4 weeks. This will give your body a chance to recover.

Then, you will start the monotherapy phase.

During the monotherapy phase, the dose and way you take Temozolomide Hexal will be different. Your doctor will work out your exact dose. There may be up to 6 treatment periods (cycles). Each one lasts 28 days. You will take your new dose of Temozolomide Hexal alone once daily for the first

5 days ("dosing days") of each cycle. The first dose will be 150 mg/m^2. Then you will have 23 days without Temozolomide Hexal. This adds up to a 28-day treatment cycle.

After Day 28, the next cycle will begin. You will again take Temozolomide Hexal once daily for 5 days followed by 23 days without Temozolomide Hexal. The Temozolomide Hexal dose may be adjusted, delayed or stopped depending on your blood counts and how you tolerate your medicine during each treatment cycle.

Patients with tumours that have returned or worsened (malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma) taking Temozolomide Hexal only:

A treatment cycle with Temozolomide Hexal lasts 28 days.

You will take Temozolomide Hexal alone once daily for the first 5 days. This daily dose depends on whether or not you have received chemotherapy before.

If you have not been previously treated with chemotherapy, your first dose of Temozolomide Hexal will be 200 mg/m^2 once daily for the first 5 days. If you have been previously treated with chemotherapy, your first dose of Temozolomide Hexal will be 150 mg/m^2 once daily for the first 5 days.

Then, you will have 23 days without Temozolomide Hexal. This adds up to a 28-day treatment cycle.

After Day 28, the next cycle will begin. You will again receive Temozolomide Hexal once daily for 5 days, followed by 23 days without Temozolomide Hexal.

Before each new treatment cycle, your blood will be tested to see if the Temozolomide dose needs to be adjusted. Depending on your blood test results, your doctor may adjust your dose for the next cycle.

How to take Temozolomide Hexal

Take your prescribed dose of Temozolomide Hexal once a day, preferably at the same time each day.

Take the capsules on an empty stomach; for example, at least one hour before you plan to eat breakfast. Swallow the capsule(s) whole with a glass of water. Do not open, crush or chew the capsules. If a capsule is damaged, avoid contact of the powder with your skin, eyes or nose. If you accidentally get some in your eyes or nose, flush the area with water.

Depending on the prescribed dose, you may have to take more than one capsule together, eventually with different strengths (content of active substance, in mg). The colour of the capsule cap is different for each strength (see in the table below).

Strength	Colour of the cap
Temozolomide Hexal **5 mg** hard capsules	green
Temozolomide Hexal **20 mg** hard capsules	yellow
Temozolomide Hexal **100 mg** hard capsules	pink
Temozolomide Hexal **140 mg** hard capsules	blue
Temozolomide Hexal **180 mg** hard capsules	maroon
Temozolomide Hexal **250 mg** hard capsules	white

You should make sure you fully understand and remember the following:

- how many capsules you need to take every dosing day. Ask your doctor or pharmacist to write it down (including the colour).
- which days are your dosing days.

Review the dose with your doctor each time you start a new cycle, since it may be different from the last cycle.

Always take Temozolomide Hexal exactly as your doctor has told you. It is very important to check with your doctor or pharmacist if you are not sure. Errors in how you take this medicine may have serious health consequences.

If you take more Temozolomide Hexal than you should
If you accidentally take more Temozolomide Hexal capsules than you were told to, contact your doctor or pharmacist or nurse immediately .

If you forget to take Temozolomide Hexal
Take the missed dose as soon as possible during the same day. If a full day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose, unless your doctor tells you to do so.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor **immediately** if you have any of the following:
- a severe allergic (hypersensitive) reaction (hives, wheezing or other breathing difficulty),
- uncontrolled bleeding,
- seizures (convulsions),
- fever,
- chills
- severe headache that does not go away.

Temozolomide Hexal treatment can cause a reduction in certain kinds of blood cells. This may cause you to have increased bruising or bleeding, anaemia (a shortage of red blood cells), fever, and reduced resistance to infections. The reduction in blood cell counts is usually short-lived. In some cases, it may be prolonged and may lead to a very severe form of anaemia (aplastic anaemia). Your doctor will monitor your blood regularly for any changes, and will decide if any specific treatment is needed. In some cases, your Temozolomide Hexal dose will be reduced or treatment stopped.

Other side effects that have been reported are listed below:

Very common (may affect more than 1 in 10 people):
- loss of appetite, difficulty speaking,headache
-
- vomiting, nausea, diarrhoea, constipation
- rash, hair loss,
- tiredness.

Common (may affect up to 1 in 10 people):
- infections, oral infections, wound infection
- reduced number of blood cells (neutropenia, thrombocytopenia, lymphopenia)
- allergic reaction
- increased blood sugar
- memory impairment, depression, anxiety, confusion, inability to fall asleep or stay asleep

- impaired coordination and balance
- difficulty concentrating, change in mental status or alertness, forgetfulness
- dizziness, impaired sensations, tingling sensation, shaking, abnormal taste
- partial loss of vision, abnormal vision, double vision, dry or painful eyes
- deafness, ringing in the ears, earache
- blood clot in lung or legs, high blood pressure
- pneumonia, shortness of breath, bronchitis, cough, inflammation of your sinuses
- stomach or abdominal pain, upset stomach/heartburn, difficulty swallowing
- dry skin, itching
- muscle damage, muscle weakness, muscle aches and pain
- painful joint, back pain
- frequent urination, difficulty withholding your urine
- fever, flu-like symptoms, pain, feeling unwell, a cold or the flu
- fluid retention, swollen legs
- liver enzyme elevations
- loss of weight, weight gain
- radiation injury
-

Uncommon (may affect up to 1 in 100 people):
- brain infections (meningoencephalitis herpetic) including fatal cases
- new or reactivated cytomegalovirus infections
- reactivated hepatitis B virus infections
- secondary cancers including leukaemia
- reduced blood cell counts (pancytopenia, anaemia, leukopenia)
- red spots under the skin
- diabetes insipidus (symptoms include increased urination and feeling thirsty), low potassium level in the blood
- mood swings, hallucination
- partial paralysis, change in your sense of smell
- hearing impairment, infection of the middle ear
- palpitations (when you can feel your heart beat), hot flushes
- swollen stomach, difficulty controlling your bowel movements, haemorrhoids, dry mouth
- hepatitis and injury to the liver (including fatal liver failure), cholestasis, increased bilirubin
- blisters on body or in mouth, skin peeling, skin eruption, painful reddening of the skin, severe rash with skin swelling (including palms and soles)
- increased sensitivity to sunlight, urticaria (hives), increased sweating, change in skin colour
- difficulty in urinating
- vaginal bleeding, vaginal irritation, absent or heavy menstrual periods, breast pain, sexual impotence
- shivering, face swelling, discolouration of the tongue, thirst, tooth disorder

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse.This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Temozolomide Hexal

Keep this medicine out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.
Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

Bottle
Do not store above 25°C
Store in the original package.
Keep the bottles tightly closed in order to protect from moisture.

Sachet
Do not store above 25°C

Tell your pharmacist if you notice any change in the appearance of the capsules.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Temozolomide Hexal contains

- The active substance is temozolomide.

  Temozolomide Hexal 5 mg hard capsules
  Each capsule contains 5 mg temozolomide.

  Temozolomide Hexal 20 mg hard capsules
  Each capsule contains 20 mg temozolomide.

  Temozolomide Hexal 100 mg hard capsules
  Each capsule contains 100 mg temozolomide.

  Temozolomide Hexal 140 mg hard capsules
  Each capsule contains 140 mg temozolomide.

  Temozolomide Hexal 180 mg hard capsules
  Each capsule contains 180 mg temozolomide.

  Temozolomide Hexal 250 mg hard capsules
  Each capsule contains 250 mg temozolomide.

- The other ingredients of the capsule are

  Temozolomide Hexal 5 mg hard capsules
  - *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.
  - *Capsule shell:* gelatine, titanium dioxide (E 171), yellow iron oxide (E 172), indigo carmine (E 132), water.
  - *Printing ink:* shellac, black iron oxide (E 172), potassium hydroxide.

  Temozolomide Hexal 20 mg hard capsules
  - *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.
  - *Capsule shell:* gelatine, titanium dioxide (E 171), yellow iron oxide (E 172), water.
  - *Printing ink:* shellac, black iron oxide (E 172), potassium hydroxide.

  Temozolomide Hexal 100 mg hard capsules
  - *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.

- *Capsule shell:* gelatine, titanium dioxide (E 171), red iron oxide (E 172), water.
- *Printing ink:* shellac, black iron oxide (E 172), potassium hydroxide.

Temozolomide Hexal 140 mg hard capsules
- *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.
- *Capsule shell:* gelatine, titanium dioxide (E 171), indigo carmine (E 132), water.
- *Printing ink:* shellac, black iron oxide (E 172), potassium hydroxide.

Temozolomide Hexal 180 mg hard capsules
- *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.
- *Capsule shell:* gelatine, titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), water.
- *Printing ink:* shellac, black iron oxide (E 172), potassium hydroxide.

Temozolomide Hexal 250 mg hard capsules
- *Capsule content:* anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.
- *Capsule shell:* gelatine, titanium dioxide (E 171), water.
- *Printing ink:* contains shellac, black iron oxide (E 172), potassium hydroxide.

What Temozolomide Hexal looks like and contents of the pack

Bottle
The hard capsules are dispensed in amber glass bottles (Type 3 glass) with polypropylene child-resistant closures. Each bottle contains either 5 or 20 capsules. The bottles also contain a desiccant pouch. Keep the desiccant pouch in the bottle. Do not swallow it.

Multipack (bottles)
Multipack containing 20 hard capsules (4 packs of 5 hard capsules in an amber glass bottle [Type 3 glass] with polypropylene child-resistant closure. The bottles contain a desiccant pouch. Keep the desiccant pouch in the bottle. Do not swallow it.)

Sachet
Each hard capsule (capsule) is individually packed in a sachet. Each carton contains 5 or 20 hard capsules.

Not all pack sizes may be marketed.

Temozolomide Hexal 5 mg hard capsules
The hard capsules have a white coloured body, a **green coloured cap**, and are imprinted with black ink. The cap is imprinted with “TMZ” and the body is imprinted with “5”.
Each capsule is approximately 15.8 mm in length.

Temozolomide Hexal 20 mg hard capsules
The hard capsules have a white coloured body, a **yellow coloured cap**, and are imprinted with black ink. The cap is imprinted with “TMZ” and the body is imprinted with “20”.
Each capsule is approximately 11.4 mm in length.

Temozolomide Hexal 100 mg hard capsules
The hard capsules have a white coloured body, a **pink coloured cap**, and are imprinted with black ink. The cap is imprinted with “TMZ” and the body is imprinted with “100”.
Each capsule is approximately 15.8 mm in length.
Temozolomide Hexal 140 mg hard capsules
The hard capsules have a white coloured body, a transparent **blue coloured cap**, and are imprinted with black ink. The cap is imprinted with “TMZ” and the body is imprinted with “140”.

Each capsule is approximately 19.3 mm in length.

Temozolomide Hexal 180 mg hard capsules
The hard capsules have a white coloured body, a **maroon coloured cap**, and are imprinted with black ink. The cap is imprinted with "TMZ" and the body is imprinted with "180".
Each capsule is approximately 19.3 mm in length.

Temozolomide Hexal 250 mg hard capsules
The hard capsules have a white coloured body, a **white coloured cap**, and are imprinted with black ink. The cap is imprinted with "TMZ" and the body is imprinted with "250".
Each capsule is approximately 21.4 mm in length.

Marketing Authorisation Holder
Hexal AG
Industriestraße 25
83607 Holzkirchen
Germany

Manufacturer
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
D-39179 Barleben
Germany

Lek Pharmaceuticals d.d
Verovskova 57
SL-1526 Ljubljana
Slovenia

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Sandoz N.V.
Telecom Gardens
Medialaan 40
B-1800 Vilvoorde
Tél/Tel: +32 (0)2 722 97 97

България
КЧТ Сандоз България
Бул."Никола Вапцаров" No. 55
сгр. 4, ет. 4
1407 София
Тел.: +359 2 970 47 47
regaffairs.bg@sandoz.com

Česká republika
Sandoz s.r.o.
Na Pankráci 1724/129
CZ-140 00, Praha 4
Tel: +420 225 775 111
office.cz@ sandoz.com

Lietuva
Sandoz Pharmaceuticals d.d
Branch Office Lithuania
Seimyniskiu 3A
LT – 09312 Vilnius
Tel: +370 5 2636 037

Luxembourg/Luxemburg
HEXAL AG
Industriestraße 25
D-83607 Holzkirchen
Tél/Tel: +49 39205 42-1305
dra.co_de@hexal.com

Magyarország
Sandoz Hungária Kft.
Bartók Béla út 43-47
H-1114 Budapest
Tel: +36 1 430 2890
Info.hungary@sandoz.com

Danmark
Sandoz A/S
Edvard Thomsens Vej 14
DK-2300 København S
Danmark
Tlf: +45 6395 1000
info.danmark@sandoz.com

Deutschland
Hexal AG
Industriestr. 25
D-83607 Holzkirchen
Tel: +49 39205 42-1305
dra.co_de@hexal.com

Eesti
Sandoz d.d. Eesti filiaal
Pärnu mnt 105
EE – 11312 Tallinn
Tel: +372 6652405

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 2811712

España
Sandoz Farmacéutica, S.A
Centro Empresarial Parque Norte
C/ Serrano Galvache Nº 56, Edificio Roble
E-28033 Madrid
Tel: +34 91 602 30 62
registros.spain@sandoz.com

France
Sandoz SAS
49, avenue Georges Pompidou
F-92593 Levallois-Perret Cedex
Tél: +33 1 49 64 48 00
regaff.france@sandoz.com

Hrvatska
Sandoz d.o.o.
Maksimirska 120
HR – 10 000 Zagreb
Tel : +385 1 235 3111

Ireland
Rowex Ltd
Newtown

Malta
Sandoz Pharmaceuticals d.d.
Verovskova 57,
SI-1000 Ljubljana
Slovenia
Tel: +356 21222872

Nederland
Sandoz B.V.
Veluwezoom 22
NL-1327 AH Almere
Tel: +31 (0)36 5241600
nl.registration@sandoz.com

Norge
Sandoz A/S
Edvard Thomsens Vej 14
DK-2300 København S
Danmark
Tlf: +45 6395 1000
info.danmark@sandoz.com

Österreich
Sandoz GmbH
Biochemiestr. 10
A-6250 Kundl
Tel: +43(0)1 86659-0
registration.vienna@sandoz.com

Polska
Sandoz Polska Sp. z o.o.
ul. Domaniewska 50 C
PL – 02 672 Warszawa
Tel.: +48 22 209 7000
maintenance.pl@sandoz.com

Portugal
Sandoz Farmacêutica Lda.
Avenida Professor Doutor Cavaco Silva, n.º 10E
Taguspark
P-2740–255 Porto Salvo
Tel: +351 21 196 40 42
regaff.portugal@sandoz.com

România
SC Sandoz S.R.L.
Strada Livezeni Nr. 7a
540472 Târgu Mureș
Tel: +40 21 407 51 60
regaffairs.ro@sandoz.com

Slovenija
Lek Pharmaceuticals d.d.
Verovškova 57

Bantry
Co. Cork
Ireland
Tel: +353 27 50077
regulatorygroup@rowa-pharma.ie

Ísland
Sandoz A/S
Edvard Thomsens Vej 14
DK-2300 Kaupmaannahöfn S
Danmörk
Tlf: +45 6395 1000
info.danmark@sandoz.com

Italia
Sandoz S.p.A.
Largo Umberto Boccioni, 1
I-21040 Origgio / VA
Tel: +39 02 96 54 1
regaff.italy@sandoz.com

Κύπρος
Sandoz Pharmaceuticals d.d.
Verovskova 57,
SI-1000 Ljubljana
Σλοβενία
Τηλ: +357 22 69 0690

Latvija
Sandoz d.d. Latvia filiāle
K.Valdemāra 33 – 29
LV-1010 Rīga
Tel: +371 67892006

SI-1526 Ljubljana
Tel: +386 1 580 21 11
Info.lek@sandoz.com

Slovenská republika
Sandoz d.d. - organizačná zložka
Žižkova 22B,
811 02 Bratislava
Tel: +421 2 48 200 600
sk.regulatory@sandoz.com

Suomi/Finland
Sandoz A/S
Edvard Thomsens Vej 14
DK-2300 Kööpenhamina S
Tanska
Puh: + 358 010 6133 400
info.suomi@sandoz.com

Sverige
Sandoz A/S
Edvard Thomsens Vej 14
DK-2300 Köpenhamn S
Danmark
Tel: +45 6395 1000
info.sverige@sandoz.com

United Kingdom (Northern Ireland)
Sandoz GmbH
Biochemiestr. 10
A-6250 Kundl
Tel: +43 5338 2000

This leaflet was last revised in <{MM/YYYY}>.

Other sources of information

Detailed information on this medicine is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/