SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIDIZOL 100 mg Capsules
Cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Temozolomide ..... 100 mg
Excipient(s):
Anhydrous lactose (from cow's milk) ..... 175.7 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Hard capsule
A hard gelatin capsule filled with powder, featuring an opaque pink cap and a white body marked with '100 mg'.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MIDIZOL is indicated for the treatment of newly diagnosed glioblastoma multiforme in the first line, in combination with radiotherapy and subsequently.

MIDIZOL is indicated for the treatment of malignant glioma patients, such as those with glioblastoma multiforme or anaplastic astrocytoma, who have relapsed or progressed after standard therapy.

MIDIZOL is indicated for the treatment of patients with metastatic malignant melanoma.

4.2. Posology and method of administration

Posology/ frequency and duration of administration:
MIDIZOL should only be used when prescribed by doctors specialising in brain tumours.

MIDIZOL should be administered at least one hour before meals, on an empty stomach. Antiemetic treatment may be administered before or after administration.

MIDIZOL treatment may be continued for a maximum of 2 years until disease progression.

Adult patients with newly-diagnosed glioblastoma multiforme
Concomitant phase:

MIDIZOL is administered orally at a dose of 75 $^{mg/m^2}$ daily for 42 days concurrently with radiotherapy (60 Gy in 30 fractions), followed by 6 courses of adjuvant therapy. Dose reduction is not recommended; however, the dose may be interrupted depending on the patient's tolerance. If all of the following conditions are met, the concurrent period with MIDIZOL may be extended from 42 days to 49 days:

- absolute neutrophil count ≥ 1.5 x 10^9/l;
- platelet count ≥ 100 × 10^9/l;
- general toxicity criteria (CTC) non-haematological toxicity ≤ grade 1 (excluding alopecia, nausea and vomiting).

A complete blood count should be performed weekly during treatment. The MIDIZOL dose during the concurrent phase should be interrupted or discontinued according to the haematological and non-haematological toxicity criteria specified in Table 1.

Table 1 Suspension of MIDIZOL Dosage During Concurrent MIDIZOL and Radiotherapy or Discontinuation of MIDISOL Dosage

Toxicity	**TMZ Dose Interrupted[a]**	**TMZ Dose Discontinued**
Absolute Neutrophil Count	≥0,5 ve <1,5 x 10^9/l	<0.5 × 10^9/l
Platelet Count	≥10 and <100 × 10^9/l	<10 × 10^9/l
CTC Non-Haematological Toxicity (excluding alopecia, nausea, and vomiting)	CTC Stage 2	CTC Stage 3 or 4

a: Concomitant TMZ treatment may be continued if all of the following conditions are met: absolute neutrophil count ≥1.5 x 10^9 /l; platelet count ≥100 x 10^9 /l; CTC non-haematological toxicity ≤grade 1 (excluding alopecia, nausea and vomiting).
TMZ = Temozolomide; CTC = Common Toxicity Criteria

Adjuvant Phase (monotherapy)

Four weeks after completion of the MIDIZOL + radiotherapy phase, MIDIZOL is administered for 6 more courses as adjuvant therapy. The dose for the first course (adjuvant) is 150 mg/m^2 once daily for 5 days followed by a 23-day treatment-free interval. At the start of the second cycle, if CTC non-haematological toxicity grade ≤2 for the first cycle (excluding alopecia, nausea, and vomiting), the absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, and the platelet count ≥ 100 x 10^9/l, the dose is increased to 200 mg/m^2. If the dose is not increased in the second cycle, it should not be increased in subsequent cycles. If no toxicity occurs, the daily dose remains 200 mg/m^2 for the first 5 days of each subsequent cycle. Dose reductions during the adjuvant phase should be applied according to **Tables 2 and** 3.

A complete blood count should be performed on day 22 of treatment (21 days after the first MIDIZOL dose). The MIDIZOL dose should be reduced or discontinued according to **Table** 3.

Table 2 MIDIZOL Dose Levels for Adjuvant Therapy

Dose Level	**Dose** (mg/m^2/day)	**Notes**
-1	100	Dose is reduced for previous toxicity
0	150	Dose in the first course
1	200	If no toxicity, the dose in cycles 2–6

Table 3 Reduction and Discontinuation of MIDIZOL Dose During Adjuvant Therapy

Toxicity	**TMZ 1 Dose Level Reduced**[a]	**TMZ Discontinued**
Absolute Neutrophil Count	<1 x 10^9/L	b
Platelet Count	<50 x 10^9/L	b
CTC Non-Haematological Toxicity (excluding alopecia, nausea, vomiting)	CTC Stage 3	CTC Stage 4[b]

a: TMZ dose levels are listed in Table 2.
b: If unacceptable toxicity persists when the dose is reduced to 100 mg/m² or if the same stage 3 non-haematological toxicity (excluding alopecia, nausea, vomiting) occurs after dose reduction, TMZ should be discontinued.
TMZ = Temozolomide; CTC = Common Toxicity Criteria

Adult patients with recurrent or progressive glioma or malignant melanoma: MIDIZOL is administered orally in repeated courses every 28 days. In patients who have not previously received chemotherapy, it is administered at a dose of 200 mg/m² once daily for 5 days. In patients who have previously received chemotherapy, the starting dose is 150 mg/m² once daily,and in the second cycle, if there is no haematological toxicity, this dose is increased to 200 mg/m² once daily. On the first day of the subsequent cycle, the absolute neutrophil count (ANC) must be equal to or greater than 1.5 x 10^9/l and the platelet count must be equal to or greater than 100 x 10^9/l. Dose modifications for MIDIZOL based on toxicity should be made according to the lowest absolute neutrophil and platelet counts.

Paediatric patients with recurrent or progressive glioma: In patients aged three years and older, MIDIZOL is administered orally at a dose of 200 mg/m² for 5 days in repeated courses every 28 days. In paediatric patients who have previously received chemotherapy, the starting dose should be 150 mg/m² once daily for 5 days, and if there is no haematological toxicity, the dose should be increased to 200 mg/m² once daily for 5 days in the next course.

Laboratory parameters for dose adjustments in recurrent or progressive malignant glioma or malignant melanoma: Before adjusting the drug dose, the following laboratory parameters must be present: Absolute neutrophil count (ANC) >1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. A complete blood count should be performed on day 22 (21 days after the first dose) or within 48 hours thereafter and repeated weekly until the absolute neutrophil count is 1.5 x 10^9/L and the

platelet count is 100 x 10^9/L. If, during any treatment cycle, the absolute neutrophil count falls below 1 x 10^9/L or the platelet count falls below 50 x 10^9/L, the dose level should be reduced by one step (50 mg/m²) in the following cycle. The dose level steps are 100 mg/m², 150 mg/m²and 200 mg/m². The recommended minimum dose is 100 mg/m².

Method of administration:
The capsules should be taken orally. If vomiting occurs after MIDIZOL administration, a second dose should not be given on the same day.

- MIDIZOL should be taken on an empty stomach (at least one hour before a meal).
- The capsules should be swallowed with a glass of water.
- The capsules should not be opened or chewed.
- The dose should be provided with the minimum number of capsules possible.
- If the capsule is damaged, avoid contact between the capsule's powder contents and the skin or mucous membranes. If contact occurs, the area should be thoroughly washed.

Additional information for specific populations:
Renal/Hepatic impairment:
The pharmacokinetics of temozolomide are comparable in patients with normal hepatic function and in patients with mild or moderate hepatic dysfunction.

There are no data available on the administration of MIDIZOL in patients with severe hepatic impairment (Child-Pugh Classification: Category C) or renal impairment. Based on the pharmacokinetic properties of temozolomide, no dose reduction is required in patients with severe hepatic impairment or renal impairment of any degree. However, caution should be exercised when administering MIDIZOL to these patients.

Paediatric population:
There is no clinical experience with MIDIZOL in children under 3 years of age. Experience in children over 3 years of age is limited. There is no clinical experience with its use in patients under 18 years of age with malignant melanoma (see Sections 4.4 and 5.1).

Efficacy and safety have not been established in children under 3 years of age.

Geriatric population:
According to pharmacokinetic analyses in the population aged 19-78 years, temozolomide clearance is not affected by age. However, elderly patients over 70 years of age have a higher risk of neutropenia and thrombocytopenia compared to younger patients (see Section 4.4). Therefore, caution should be exercised when using MIDIZOL in elderly patients.

4.3. Contraindications
MIDIZOL,

- Hypersensitivity to the active substance or any of the excipients listed in Section 6.1,

- Hypersensitivity to dacarbazine (DTIC),
- It is contraindicated in patients with 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 hepatitis B virus (HBV), cytomegalovirus (CMV)) have been observed during treatment with temozolomide (see Section 4.8).

***Pneumocystis jirovecii* pneumonia**

A pilot study demonstrated that patients receiving temozolomide and radiotherapy concurrently with an extended 42-day regimen were at particular risk of developing *Pneumocystis jirovecii* pneumonia (PCP). Therefore, all patients receiving concurrent MIDIZOL and radiotherapy in a 42-day (maximum 49-day) regimen should receive prophylaxis for PCP, regardless of lymphocyte count. If lymphopenia occurs, patients should continue prophylaxis until lymphopenia regresses to Stage ≤1.

The incidence of PCP may increase when temozolomide is used in a longer-term dosing regimen. However, all patients receiving temozolomide, especially those using steroids, should be closely monitored for PCP regardless of the dosing regimen. Cases of fatal respiratory failure have been reported in patients receiving temozolomide in combination with dexamethasone or other steroids.

HBV

In some fatal cases, hepatitis associated with hepatitis B virus (HBV) reactivation has been reported. Patients with positive hepatitis B serology (including those with active disease) should be referred to specialists in liver disease before starting treatment. Patients should be monitored and treated appropriately during treatment.

Herpetic meningoencephalitis

In post-marketing cases, including cases using concomitant steroids, herpetic meningoencephalitis (including fatal cases) has been observed in patients receiving temozolomide in combination with radiotherapy.

Hepatotoxicity

Liver damage, including fatal liver failure, has been reported in patients treated with temozolomide (see Section 4.8). Liver function tests should be performed prior to initiating treatment. If these tests are abnormal, physicians should evaluate the risk/benefit ratio, including the potential for fatal hepatic failure, before initiating temozolomide. In patients receiving a 42-day treatment cycle, liver function tests should be repeated in the middle of the cycle. Liver function tests should be performed after each treatment cycle in all patients. In patients with significant liver function abnormalities, physicians should evaluate the

risk/benefit ratio of continuing treatment. Liver toxicity may occur several weeks after the last temozolomide treatment or later.

Malignancies
Very rarely, cases of myelodysplastic syndrome, including myeloid leukaemia, and secondary malignancies have been reported (see Section 4.8).

Anti-emetic treatment
Nausea and vomiting are very commonly observed with MIDIZOL treatment. Antiemetic treatment may be administered before or after MIDIZOL administration.

For newly diagnosed adult patients with glioblastoma multiforme:
Anti-emetic prophylaxis is recommended prior to the initial dose of the concurrent phase and is strongly recommended during the monotherapy phase.

Patients with recurrent or progressive malignant glioma:
Anti-emetic treatment may be required in patients who experienced severe (grade 3 or 4) vomiting during previous treatment cycles.

Laboratory parameters:
Patients treated with MIDIZOL may experience myelosuppression, including prolonged pancytopenia; in some cases, this may lead to aplastic anaemia, which can be fatal. In some cases, concomitant exposure to medicinal products associated with aplastic anaemia, such as carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates the assessment. The following laboratory parameters must be met prior to treatment: MNS $\geq$ 1.5 x10^9/l and platelet count $\geq$ 100 x 10^9/l. A complete blood count should be performed 21 days after the first dose (on day 22) or within 48 hours thereafter, and weekly complete blood counts should be performed until MNS exceeds 1.5 x 10^9/l and platelet count exceeds 100 x 10^9/l. If MNS falls below 1 x 10^9/l or the platelet count falls below 50 x 10^9/l in any cycle, the dose level should be reduced by one level in the next cycle (see Section 4.2). Dose levels are 100 mg/m², 150 mg/m² and 200 mg/m². The recommended minimum dose is 100 mg/m².

Paediatric use:
There is no clinical experience with MIDIZOL use in children under 3 years of age. Experience in older children and adolescents is very limited (see Sections 4.2 and 5.1).

Use in elderly patients (aged 70 years and over):
The risk of neutropenia and thrombocytopenia is higher in elderly patients than in younger patients. Therefore, caution should be exercised when using MIDIZOL in elderly patients.

Female patients

Women of childbearing potential should use effective contraception to avoid pregnancy during treatment with MIDIZOL and for at least 6 months following completion of treatment.

Male patients:
Male patients treated with MIDIZOL are advised to avoid fathering children for at least 3 months after the last dose and to seek advice on sperm cryopreservation prior to treatment (see Section 4.6).

Lactose:
MIDIZOL contains 175.7 mg of anhydrous lactose per capsule. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction
In a separate Phase I study, the administration of temozolomide with ranitidine did not result in changes in the absorption rate of temozolomide or exposure to its active metabolite, monomethyl triazenoimidazole carboxamide (MTIC).
When temozolomide was administered with food, a 33% decrease in C_{max} and a 9% decrease in AUC were observed. As the change in C_{max} cannot be considered clinically insignificant, MIDIZOL should not be administered with food.

Based on an analysis of population pharmacokinetics in Phase II studies, co-administration with dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 receptor antagonists, or phenobarbital does not alter the clearance of temozolomide. When administered concomitantly with valproic acid, there is a small but statistically significant decrease in temozolomide clearance.

No studies have been conducted to determine the effects of temozolomide on the metabolism or elimination of other medicinal products. However, as temozolomide is not metabolised in the liver and has a low protein binding, it is unlikely to affect the pharmacokinetics of other medicinal products (see Section 5.2).

The combined use of temozolomide with other myelosuppressive agents may increase the likelihood of myelosuppression.

<u>Paediatric population</u>
Interaction studies have only been conducted in adults.

4.6. Pregnancy and lactation
Pregnancy category: D

Women of childbearing potential/Contraception

Women of childbearing potential should use an effective method of contraception while taking MIDIZOL and for at least 6 months after completing treatment to avoid pregnancy.

Pregnancy
There are no data available on the use of MIDIZOL in pregnant women. In preclinical studies in mice and rabbits receiving 150 $^{mg/m^2}$temozolomide, teratogenicity and/or fetal toxicity has been demonstrated (see Section 5.3). MIDIZOL should not be administered to pregnant women. If use during pregnancy is considered, the patient should be informed of the potential risk to the foetus.

Lactation
As it is unknown whether MIDIZOL passes into breast milk, MIDIZOL should not be used in breastfeeding women.

Reproductive ability/Fertility
Toxicity has been demonstrated in the male reproductive system in rats and dogs (see Section 5.3).

Male fertility
Temozolomide may have genotoxic effects. Therefore, men treated with temozolomide should use effective contraceptive measures, should not father a child for at least 3 months after the last dose, and should consider cryopreserving their sperm prior to treatment due to the possibility of irreversible infertility associated with temozolomide therapy.

4.7. Effects on the ability to drive and use machinery
MIDIZOL may have a mild effect on the ability to drive and use machines due to drowsiness and sleepiness (see Section 4.8).

4.8. Undesirable effects
Summary of safety profile
Clinical trial experience
The most commonly reported adverse reactions in clinical trials in patients treated with temozolomide were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions and rash. Most haematological adverse reactions were commonly reported; the frequency of grade 3-4 laboratory findings is presented in Table 4.

In patients with recurrent and progressive glioma, nausea (43%) and vomiting (36%) are generally grade 1 or 2 (0–5 vomiting episodes in 24 hours) and are self-limiting or easily controlled with standard antiemetic therapy. The incidence of severe nausea and vomiting is 4%.

Tabulated list of adverse reactions

Adverse reactions observed in clinical trials and reported during the post-marketing use of temozolomide are listed in Table 4.
These reactions are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following standard rates: 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 (cannot be estimated from the available data) Adverse effects are presented in descending order of severity within each frequency grouping.

Table 4. Adverse reactions reported in patients treated with temozolomide

Infections and infestations	
Common:	Infections, herpes zoster, pharyngitis[a], oral candidiasis
Uncommon:	Opportunistic infection (including PCP), sepsis†, herpetic meningoencephalitis†, CMV infection, CMV reactivation, hepatitis B virus†, herpes simplex, infection reactivation, wound infection, gastroenteritis [b]
(Including cysts and polyps) Benign and malignant neoplasms	
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
Metabolic and nutritional disorders	
Very common:	Anorexia
Common:	Hyperglycaemia
Uncommon:	Hypokalaemia, increased alkaline phosphatase
Psychiatric disorders	
Common:	Agitation, amnesia, depression, anxiety, confusion, insomnia
Uncommon:	Behavioural disorder, emotional lability, hallucinations, apathy

Nervous system disorders	
Very common:	Convulsions, hemiparesis, aphasia/dysphasia, headache
Common:	Ataxia, balance disorder, cognitive impairment, concentration disorder, decreased consciousness, dizziness, hypoesthesia, memory impairment, neurological disorder, neuropathy[d], paraesthesia, somnolence, speech disorder, change in taste sensation, tremor
Uncommon:	Status epilepticus, hemiplegia, extrapyramidal disorder, parosmia, abnormal gait, hyperaesthesia, sensory disorder, abnormal coordination
Eye disorders	
Common:	Hemianopia, blurred vision, visual impairment[e], visual field defect, diplopia, eye pain
Uncommon:	Decreased visual acuity, dry eyes
Ear and inner ear disorders	
Common:	Deafness[f], vertigo, tinnitus, ear paing[g]
Uncommon:	Hearing impairment, hyperacusis, otitis media
Cardiac disorders	
Uncommon:	Palpitations
Vascular diseases	
Common:	Haemorrhage, pulmonary embolism, deep vein thrombosis, hypertension
Uncommon:	Cerebral haemorrhage, redness in the face and neck, hot flushes
Respiratory, chest disorders and mediastinal diseases	
Common:	Pneumonia, dyspnoea, sinusitis, bronchitis, cough, upper respiratory tract 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, dry mouth
Hepatobiliary disorders	
Uncommon:	Liver failure†, liver damage, hepatitis, cholestasis, hyperbilirubinaemia
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 peeling, photosensitivity reaction, urticaria, exanthema, dermatitis, increased sweating, abnormal pigmentation
Unknown:	Drug reaction with eosinophilia and systemic symptoms reaction (DRESS)
Musculoskeletal disorders, connective tissue and bone diseases	
Common:	Myopathy, muscle weakness, arthralgia, back pain, musculoskeletal pain, myalgia
Renal and urinary disorders	
Common:	Frequent urination, 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, flu-like symptoms, asthenia, weakness, pain, oedema, peripheral oedema[i]
Uncommon:	Worsening of condition, rigidity, facial oedema, change in tongue colour, thirst, dental disease
Studies	
Common:	Elevated liver enzymes[j], weight loss, weight gain
Uncommon:	Increased gamma-glutamyltransferase
Injury, poisoning, and procedure-related complications	
Common:	Radiation-related damage[k]

[a]Includes pharyngitis, nasopharyngeal pharyngitis, and streptococcal pharyngitis

[b] Includes gastroenteritis and viral gastroenteritis

[c] Includes Cushingoid and Cushing's syndrome

[d] Includes neuropathy, peripheral neuropathy, polyneuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy

[e] Includes visual impairment and eye disease

[f] Includes deafness, bilateral deafness, sensorineural deafness, and unilateral deafness

[g] Includes ear pain and ear discomfort

[h] Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal discomfort

[i] Includes peripheral oedema and peripheral swelling

[j] Includes increased liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase, and increased liver enzymes

[k] Includes radiation damage and radiation-related skin damage

† Includes cases resulting in death

Newly diagnosed glioblastoma multiforme patients:

Laboratory results:

Myelosuppression (neutropenia and thrombocytopenia), known to be dose-limiting for most cytotoxic agents including temozolomide, has been observed. When laboratory abnormalities and adverse events were combined for the concurrent and monotherapy treatment phases, stage 3 or stage 4 neutrophil abnormalities, including neutropenic events, were observed in 8% of patients. Grade 3 or 4 platelet abnormalities, including thrombocytopenic events, were observed in 14% of patients receiving temozolomide.

Patients with recurrent or progressive malignant glioma:

Laboratory results:

Grade 3 or 4 thrombocytopenia and neutropenia were observed in 19% and 17% of patients treated for malignant glioma, respectively. This required discontinuation of temozolomide treatment and/or hospitalisation in 8% and 4% of patients, respectively. Myelosuppression was predictable (usually occurring during the first few cycles, with nadir observed between days 21 and 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 the population pharmacokinetic analysis of the clinical trial experience, the lowest absolute neutrophil count was recorded in 101 female and 169 male patients, and the lowest absolute platelet count was recorded in 110 female and 174 male patients. Stage 4 neutropenia (MNS < 0.5 x 10^9 /l) was observed in 12% of women and 5% of men during the first cycle of treatment, while thrombocytopenia (< 20 x 10^9/l) was observed in 9% of women and 3% of men. In a dataset of 400 patients with recurrent glioma, Stage 4 neutropenia developed in 8% of women and 4% of men during the first cycle of treatment, while Stage 4 thrombocytopenia developed in 8% of women and 3% of men. In a study involving 288 patients newly diagnosed with glioblastoma multiforme, Stage 4 neutropenia was observed in 3% of women and 0% of men during the first course of treatment. Stage 4 thrombocytopenia was observed in 1% of women and 0% of men.

Paediatric population

Oral temozolomide has been studied in a regimen administered for 5 days every 28 days in paediatric patients (aged 3-18 years) with recurrent brainstem glioma or recurrent high-grade astrocytoma. Although data are limited, tolerance in children is expected to be similar to that in adults. The safety of temozolomide in children under 3 years of age has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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.

4.9. Overdose

Doses of 500, 750, 1000 and 1250 mg/m²(total dose per course over 5 days) have been clinically investigated in patients. The dose-limiting toxicity is haematological toxicity, which has been reported at many doses but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose over a single 5-day course) has been reported in one patient. Adverse effects reported include pancytopenia, pyrexia, multiple organ failure, and death. In patients receiving the recommended dose for longer than 5 days (up to 64 days), bone marrow suppression with or without infection has been reported, which in some cases was severe and prolonged and resulted in death. Haematological monitoring is required in cases of overdose. Supportive treatment should be administered 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 triazine that undergoes rapid chemical conversion at physiological pH to form the active component monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to result primarily from alkylation at the O^6 position of guanine and, additionally, from alkylation at the N^7 position. The resulting cytotoxic lesions are thought to be related to abnormal repair of methyl involvement.

Clinical efficacy and safety

Newly diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive temozolomide + RT (n=287) or RT alone (n=286). Patients in the temozolomide + RT arm received temozolomide (75 mg/m²) once daily concomitantly with RT for 42 days (maximum 49 days) from the first day of RT until the last day of RT. This was followed by temozolomide monotherapy (150–200 mg/m²) administered on days 1–5 of each 28-day cycle for up to 6 cycles, starting 4 weeks after the completion of RT. Patients in the control arm received RT alone. Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) was required during RT and combined temozolomide treatment.

Of the 282 patients in the RT-only arm, 161 (57%) received temozolomide as rescue therapy during follow-up, as did 62 (22%) of the 277 patients in the temozolomide + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95% confidence interval (CI) for HR = 1.33–1.91) and the log-rank p-value was < 0.0001 in favour of the temozolomide arm. The calculated probability of survival for 2 years or longer (10% vs. 26%) was higher in the RT +

Temozolomide arm. The addition of concurrent temozolomide to RT followed by temozolomide monotherapy in the treatment of newly diagnosed glioblastoma multiforme patients showed a statistically significant improvement in overall survival (OS) compared to RT alone (Figure 1).

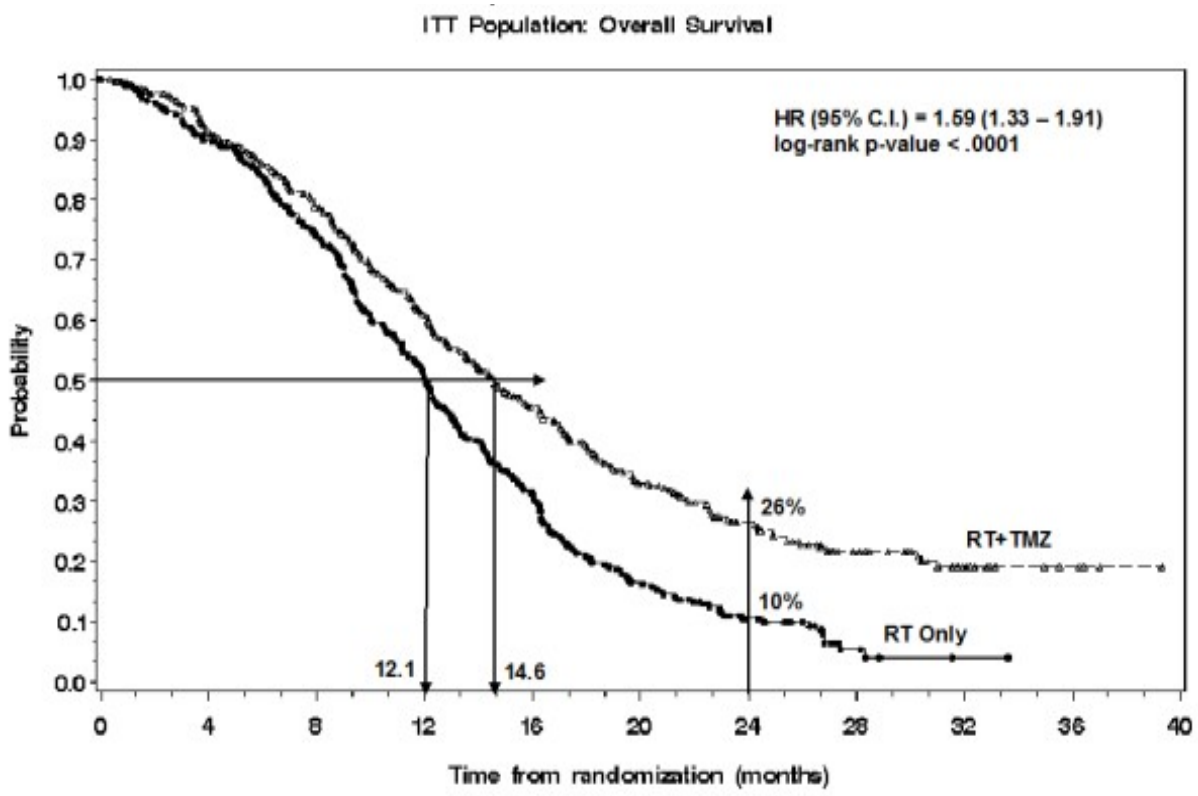

Figure 1. Kaplan-Meier curves for overall survival (ITT (intent-to-treat) population)

The study results are inconsistent in a subgroup of patients with poor performance status (WHO PS=2, n=70), and overall survival and time to progression are similar in both arms in this subgroup. However, it is understood that there are no unacceptable risks in this patient group.

Recurrent or progressive malignant glioma

Clinical efficacy data in patients with glioblastoma multiforme who progressed or relapsed after surgery and RT (Karnofsky performance status [KPS] ≥ 70) are based on two clinical trials conducted with oral temozolomide. One was a non-comparative study in 138 patients (29% had received prior chemotherapy), and the other was a randomised, active-controlled study in a total of 225 patients (67% had received prior nitrosourea-based chemotherapy) comparing temozolomide with procarbazine. In both studies, the primary endpoint was progression-free survival (PFS), defined as magnetic resonance imaging or neurological deterioration. In the non-comparative study, PFS at 6 months was 19%, the median progression-free survival was 2.1 months, and the median overall survival was 5.4 months. The objective response rate (ORR) based on MRI scans was 8%.

In a randomised, active-controlled study, PFS at 6 months was significantly higher with temozolomide than with procarbazine (21% vs 8% – chi-square p = 0.008), and median PFS was 2.89 months and 1.88 months, respectively (log-rank p = 0.0063). The median survival time for temozolomide and procarbazine was 7.34 months and 5.66 months, respectively (log-rank p = 0.33). At six months, the proportion of patients alive in the temozolomide arm (60%) was significantly higher than in the procarbazine arm (44%) (chi-square p = 0.019). Benefit was demonstrated in patients with KPS ≥ 80 who had previously received chemotherapy.

Data on time to neurological deterioration and time to performance status deterioration favoured temozolomide over procarbazine (decline in KPS to < 70 or a decrease of at least 30 points). The median times to progression at these endpoints are 0.7–2.1 months longer with temozolomide compared to procarbazine (log-rank p = < 0.01–0.03).

Recurrent anaplastic astrocytoma
In a multicentre, prospective phase II study evaluating the safety and efficacy of oral temozolomide in the first relapse of patients with anaplastic astrocytoma, PFS was 46% at 6 months and median PFS was 5.4 months. The median overall survival was 14.6 months. The response rate based on the investigator's assessment of central review was 35% in the intention-to-treat (ITT) population (n=162) (13 complete responses and 43 partial responses). Stable disease was reported in 43 patients. The 6-month event-free survival rate in the ITT population is 44% and the median event-free survival time is 4.6 months; these figures are similar to the progression-free survival results. Efficacy results are similar in the histology-qualified population. Achieving radiological objective response or maintaining progression-free status was strongly associated with maintaining or improving quality of life.

Paediatric patients:
Oral temozolomide was studied in paediatric patients (aged 3-18 years) with recurrent brainstem glioma or recurrent high-grade astrocytoma in a regimen of daily administration for 5 days every 28 days. Tolerance to temozolomide is similar to that in adults.

5.2. Pharmacokinetic properties

General characteristics
Temozolomide spontaneously hydrolyses at physiological pH to its active form, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC). MTIC spontaneously hydrolyses to 5-amino-imidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and methylhydrazine, believed to be the active alkylating species. The cytotoxicity of MTIC is thought to arise primarily from DNA alkylation, mainly at the $O^6$and N^7positions of guanine. Exposure to MTIC and AIK is ~2.4% and 23%, respectively, compared to temozolomide AUC. Under *in vivo* conditions, the $t_{1/2}$of MTIC is similar to that of temozolomide (1.8 hours).

Absorption:

Following oral administration in adult patients, temozolomide is rapidly absorbed and reaches peak concentration within a short time (20 minutes) after dosing (mean time 0.5 to 1.5 hours). Following oral administration of ^{14}C-labelled temozolomide, the mean excretion rate of ^{14}C over 7 days after dosing was 0.8%, indicating complete absorption.

Distribution:
Temozolomide binds to proteins to a low extent (10–20%) and is not expected to interact with highly protein-bound substances.

Preclinical data and PET studies in humans suggest that temozolomide rapidly crosses the blood-brain barrier and is present in cerebrospinal fluid (CSF). Penetration into cerebrospinal fluid has been confirmed in one patient, and CSF exposure based on the area under the curve is approximately 30% of that in plasma; this finding is consistent with animal data.

Biotransformation
Following oral administration, an average of 5-10% of the dose is excreted unchanged in the urine within 24 hours, with the remainder being excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites. Plasma concentrations increase in a dose-dependent manner.

Elimination:
The plasma half-life ($t_{1/2}$) is approximately 1.8 hours. Elimination of ^{14}C occurs primarily via the kidneys.

Linearity/Non-linearity:
Plasma concentrations increase in a dose-dependent manner. Plasma clearance, distribution volume, and half-life are independent of dose.

Additional information for specific populations
Population-based pharmacokinetic analysis of temozolomide showed that plasma temozolomide clearance is independent of age, renal function, or tobacco use. Another pharmacokinetic study found that patients with mild to moderate hepatic dysfunction had similar plasma pharmacokinetic profiles to patients with normal hepatic function.

The area under the curve (AUC) is greater in paediatric patients; however, the maximum tolerated dose (MTD) is 1000 mg/m² per course in both children and adults.

5.3. Preclinical safety data
Single-course (5-day dosing, 23-day drug-free period), three-course, and six-course toxicity studies were conducted in rats and dogs. The primary targets of toxicity were the bone marrow, lymphoreticular system, testes, and gastrointestinal tract, and retinal degeneration was observed at higher doses (fatal in 60-100% of rats and dogs tested). With the exception of adverse events

involving the male reproductive system and retinal degeneration, most toxicity findings were reversible. However, as the doses implicated in retinal degeneration were within the lethal dose range and no similar effect was observed in clinical studies, this finding was not considered clinically significant.

Temozolomide is an embryotoxic, teratogenic, and genotoxic alkylating agent. Temozolomide is more toxic in rats and dogs than in humans, and the clinical dose is close to the minimum lethal dose in rats and dogs. Dose-dependent decreases in leukocytes and thrombocytes are sensitive indicators of toxicity . In a six-course rat study, various neoplasms including mammary carcinomas, keratoacanthomas and basal cell adenomas were observed, but no tumours or preneoplastic changes were observed in dog studies. Rats appear to be particularly sensitive to the oncogenic effects of temozolomide, with the first tumours appearing within 3 months of starting the dose. This latent period is very short, even for an alkylating agent.

Positive mutagenic responses were observed in the results of the Ames/Salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous lactose (derived from cow's milk)
Sodium starch glycolate
Colloidal silicon dioxide
Tartaric acid
Stearic acid

Gelatin capsule composition:
Titanium dioxide
Gelatin (bovine bone gelatin)
Red iron oxide

Printing ink composition:
Glazed shellac
Black iron oxide
Propylene glycol
Ammonium hydroxide (28%)

6.2. Incompatibilities

No known incompatibilities.

6.3. Shelf life

24 months

6.4. Special precautions for storage
It should be stored at a room temperature below 25°C.

6.5. Nature and contents of container
Each capsule is contained in a blister pack made of OPA/Aluminium/PVC foil and aluminium foil. Each box contains 5 or 20 hard gelatin capsules in blister packs.

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 temozolomide 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.

Cytotoxic drugs, their secondary packages and equipment/materials used in the preparation/ administration of these drugs are considered **HAZARDOUS WASTE** and should be disposed according local regulations and guidelines.

7. MARKETING AUTHORISATION HOLDER

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