European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMA/50915/2010

ASSESSMENT REPORT

FOR

Temozolomide Teva

International Nonproprietary Name: **temozolomide**

Procedure No. EMEA/H/C/001126

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 28 January 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Temozolomide Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC.
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The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

- Product name, strength, pharmaceutical form: Temodal 5 mg hard capsules
- Marketing authorisation holder: SP Europe
- Date of authorisation: 26 January 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/98/096/001 -002

■ *Medicinal product authorised in the Community/Member State where the application is made or European reference medicinal product:*

- Product name, strength, pharmaceutical form: Temodal 5, 20, 100, 140, 180, 250 mg hard capsules
- Marketing authorisation holder: SP Europe
- Date of authorisation: 26 January 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/98/096/001 -012

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:*

- Product name, strength, pharmaceutical form: Temodal 20 and 250 mg hard capsules
- Marketing authorisation holder: SP Europe
- Date of authorisation: 26 January 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number(s): EU/1/98/096/004, 007
- Bioavailability study number(s): TEM-BESD-01-TIE/07

The Rapporteur appointed by the CHMP and the evaluation team was Tomas P Salmonson

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 28 January 2009.
- The procedure started on 25 February 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 May 2009.

- During the meeting on 22-25 June 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 June 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 24 September 2009.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 September 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 October 2009.
- During the CHMP meeting on 19-22 October 2009, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 22 October 2009.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 3 November 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 11 November 2009.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Temozolomide Teva on 19 November 2009.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 28 January 2010.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Temozolomide Teva 5, 20, 100, 140, 180, 250 mg hard capsules is a generic medicinal product containing temozolomide as active substance. The reference medicinal product Temodal 5, 20, 100, 140, 180, 250 mg hard capsules, has been centrally authorized on 26 January 1999. The active substance of the reference product is temozolomide.

Temozolomide (TMZ) is the 3-methyl derivative of mitozolomide and chemically related to another imidazole carboxamide namely dacarbazine. Both dacarbazine and TMZ are not directly active and cleave to form the linear triazene 5-(3-methyl)1-triazen-1-yl-imiazole-4- carboxamide (MTIC) which is the reactive metabolite responsible for DNA alkylation. Unlike dacarbazine, which requires metabolic dealkylation (a relatively inefficient process in humans compared to rodents) to form MTIC, TMZ undergoes rapid nonenzymatic conversion to MTIC under physiological condition. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the N^7 and ^6O positions of guanine although methylation at the ^3O position also occurs.

Temozolomide Teva is indicated for the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment. Temozolomide Teva is also indicated for the treatment of 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.

Temozolomide Teva 5, 20, 100, 140, 180, 250 mg hard capsules is administered in combination with focal radiotherapy (concomitant phase) followed by up to 6 cycles of temozolomide (Temozolomide) monotherapy (monotherapy phase).

In the concomitant phase, Temozolomide is administered orally at a dose of 75 mg/m² daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of Temozolomide administration should be decided weekly according to haematological and non-haematological toxicity criteria. Temozolomide 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) $\geq 1.5 \times 10^9$/l
- thrombocyte count $\geq 100 \times 10^9$/l
- common toxicity criteria (CTC) non-haematological toxicity $\leq$ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly.

Four weeks after completing the Temozolomide + RT concomitant phase, Temozolomide is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m² if the CTC nonhaematological toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is $\geq 1.5 \times 10^9$/l, and the thrombocyte count is $\geq 100 \times 10^9$/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/m² per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions and discontinuations during the monotherapy phase may be applied.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose of Temozolomide).

For adults 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, Temozolomide is administered orally at a dose of 200 mg/m² 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/m² once daily, to be increased in the second cycle to 200 mg/m² once daily, for 5 days if there is no haematological toxicity.

2.2 Quality aspects

Introduction

The product is presented as hard gelatin capsules containing 5, 20, 100, 140, 180 and 250 mg of temozolomide as active substance.
Other ingredients are defined in the SPC section 6.1.

The capsules are packed in glass bottles.

Active Substance

The chemical name of temozolomide is (2) 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide corresponding to the molecular formula $C_6H_6N_6O_2$ and relative molecular mass 194.15.
It appears as a white to light tan/light pink non-hygroscopic powder that is slightly soluble in water. Its dissociation constant pK_a has been found 0 and partition coefficient has been determined logP = -1.153. Temozolomide is achiral, but shows polymorphism and nine polymorphic forms have been identified. The active substance manufacturer consistently produces one polymorphic form and this is used in the manufacture of the product.

- Manufacture

An ASMF for temozolomide has been submitted. The manufacturing process of temozolomide consists of three synthetic steps followed by crystallisation. Starting materials as well as synthetic intermediates were described in sufficient detail. The critical process parameters of all stages with appropriate justification have been described.

- Specification

The drug substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR, HPLC), chloride (Ph.Eur.), loss on drying (Ph.Eur.), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC) and acetic acid (HPLC).
Batch analysis data are presented for three production scale and ten pilot scale batches manufactured by the proposed manufacturer. The batches have been tested for all parameters included in the drug substance manufacturer's specification, except for microbiological purity. All parameters evaluated comply with the specification.

- Stability

Stability data has been presented for three pilot scale batches stored under normal conditions (25°C, 60% RH) for up to 24 months, and for up to 6 months under accelerated conditions (40°C, 75% RH).
Additional stability data from three combined commercial batches for up to 18 months of storage under normal and up to 6 months under accelerated conditions were also presented.
Data from the combined batches obtained under 18 months real time and 6 months accelerated studies showed all results to comply with the proposed specification. No specific trends were evident. This was also the case for the pilot scale batches that where presented in the initial submission.

Based on the data provided to date the retest period proposed by the ASMF-holder is judged acceptable.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to formulate a conventional solid oral dosage form (hard capsule) with the dosage of 5, 20, 100, 140, 180 and 250 mg temozolomide per capsule that are essentially similar to the innovator product, Temodal.
Temozolomide is unionized (no pKa) and does not show any pH dependant solubility. The highest dose 250 mg is soluble in <250 ml over the range of pH 1-7.5 and is thus considered as highly soluble as per BCS guidance. Due to the BCS class 1 characteristic the particle size is not considered to have any impact on the dissolution properties. Only one polymorphic form is used. As only dry mixing is applied during manufacture of the drug product no change in the polymorphic form is expected.
The excipients used are the same excipients contained in the innovator product, Temodal. All excipients are commonly used in pharmaceutical oral dosage forms and comply with the Ph. Eur.
Compatibility of the excipients in the formulation and with the drug substance is confirmed by the stability studies (section IV.8)
Dissolution studies of Temozolomide Teva and the reference product were carried out at three media of different pH. It was shown that more than 85% of the drug was released in 15 minutes in all three media from all strengths of both the Temozolomide Teva and reference product.
Temozolomide Teva 5, 20, 100, 140, 180 and 250 mg hard gelatine capsules are formulated with anhydrous lactose, sodium starch glycolate, tartaric acid, colloidal anhydrous silica and stearic acid. Three powder blends are developed, one for the 5 mg and 20 mg strengths respectively and one for the 100 mg, 140 mg, 180 mg and 250 mg strengths. Temozolomide Teva capsules are packaged in amber glass bottles with child-resistant, induction sealed screw cap.
Bioequivalence studies have been submitted for the 20 mg and 250 mg strengths.
The absence of studies with the 5 mg, 100 mg, 140 mg and 180mg tablet strengths is considered acceptable for the following reasons:

- the pharmacokinetics of temozolomide is linear in the therapeutic dose range
- the different strengths are produced using the same process and by the same manufacturer
- the qualitative composition is the same for the different strengths
- the ratio between amounts of active substance and excipients is the same in the strength in the range 100 mg to 250 mg. The 5 mg strength is not dose proportional but amount of active substance is low (5%) and the ratio between excipients is similar to that of the 20 mg strength.
- the in vitro dissolution profile is similar for the different tablet strengths. Additional strengths of Temozolomide capsules; 5 mg, 20 mg, 100 mg, 140 mg and 180 mg versus the 250 mg strength were observed to be similar.
- In all media more than 85% was released after 15 minutes.

- Manufacture of the Product

The manufacturing process is a conventional process for hard capsule manufacture and involves: mixing, sieving, capsule filling and packaging.
The manufacturing process has been acceptably described. The validation results demonstrate that the manufacturing process has been appropriately validated.

- Product Specification

The product release and shelf-life specifications include tests for appearance (visual), identification (temozolomide: HPLC, UV, titanium dioxide: chemical reaction), Uniformity of dosage units (Ph. Eur.), dissolution (PhEur-UV), assay (HPLC), related substances (HPLC), water content (USP) and microbial limits (Ph.Eur. - Non-routine test).

Data are provided for two production scale batches of each dosage strength. The batches were manufacture by the proposed manufacturer using two different batches of drug substance.
Results showed all batches to meet the specification in all cases.

- Adventitious Agents

Lactose is derived from animals for which satisfactory BSE statement has been provided. The lactose conforms with the Note for Guidance EMEA/410/01 rev 2.
The gelatine of the hard capsule shells is derived from bovine raw material. Corresponding certificates of suitability from the suppliers of the gelatine were presented.

- Stability of the Product

Results from two commercial batches of 5, 20 and 100 mg (in both 5 caps and 20 mg caps containers), one batch of 140 mg, 180 mg and two batches of 250 mg stored under normal conditions (25 °C / 60% RH) and intermediate conditions (30°C / 65% RH) for 12 months have been presented.
In addition, results from two commercial batches of 5, 20 and 100 mg (in both 5 caps and 20 mg caps containers), one batch of 140 mg, 180 mg and two batches of 250 mg stored under accelerated conditions (40 °C / 75% RH) for 6 months have been presented.
For 5, 20, 100, 140 and 180 mg an increase for the known impurity was observed at intermediate conditions.
For all strengths an increase at accelerated conditions for the main degradation product was observed. Except for the 250mg formulation the values were OOS after 6 months at accelerated conditions. As this impurity is considered to be qualified as a metabolite of temozolomide the limits for the shelf life of this impurity and the Total impurities were adjusted accordingly, which is considered acceptable.
Intermediate conditions are after 12 months well within the specification for this parameter.
No significant changes of other relevant parameters like assay and dissolution have been observed at any storage condition.
Stability studies have confirmed that the polymorphic form is maintained.
One batch of each dosage strength of Temodac capsules has been tested for photostability.
Results showed the product can be considered stable against light when kept in the original container.

Based on the stability data presented up to date the shelf-life and storage condition proposed by the applicant is considered acceptable.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-Clinical aspects

There were no detailed non-clinical pharmacology, pharmacokinetics and toxicology study reports submitted by the applicant. The non-clinical studies refer to 45 publications from 1987 to 2007. The applicant submitted a justification why no additional studies are required.

Pharmacology

A review of the literature was submitted which described the pharmacologic aspects of temozolomide.

TMZ has demonstrated anti-tumour activity *in vitro* against a variety of malignancies; including glioma, metastatic melanoma, ependymoma and medulloblastoma among others. Overall the toxicity of TMZ on a range of human and murine tumour cell-lines showed a wide variation. Cell-lines which express low levels of the DNA repair protein AGT, which is known to protect cells from alkylating

damage at the ^{6}O position of guanine, show more sensitivity toward cytotoxic effects of TMZ. TMZ mediates AGT depletion and displays activity in cells that is inversely proportional to AGT activity in these cells.

The pharmacology of TMZ *in vivo* has been studied in two animal models (rat and mouse) using different mode of administration. Subcutaneous single (160mg/kg) and repeated doses (40mg/kg/day for 5 days) of TMZ in mice increased the survival time in mice with subcutaneous implanted lymphomas. 5-day treatment (40mg/kg/day) was more effective that a single dose application of 160mg/kg.

Intraperitoneal administration of TMZ demonstrated growth delay against a panel of CNS tumour xenografts including adult anaplastic astrocytoma, childhood glioblastoma multiforme, medulloblastoma. Using the intraperitoneal route of administration , TMZ was more effective when given as a single dose 0f 1200mg/m^2 compared to the repeated dosing (411mg/m^2 for 5 days). Hence, the activity of TMZ was found to be schedule dependent. The effect of TMZ (intraperitoneal dose of 411 mg/m^2/day for 5 days) on the tumour growth delays was more pronounced compared to those of procarbazine (intraperitoneal dose of 700mg/m^2/day for 5 days).

Mechanisms of Resistance

The methylation of ^{6}O position of guanine causing base pair mismatch is the primary mechanism of cytotoxicity of MTIC. Unsuccessful cycles of mismatch repair eventually lead to breaks and permanent nicks in the daughter strand and preventing mitotic division and the cell undergoes apoptosis. The enzyme alkylguanine alkyltransferase (AGT) is responsible for removing the alkyl group from the ^{6}O position of guanine and hence reversing the cytotoxic lesion of TMZ. Additionally, deficiency in the mismatch repair which results in the failure to recognition and repair of the ^{6}O methylguanine (^{6}O-MG) adducts render cells tolerant to methylation and to cytotoxic effects of TMZ since in these cells DNA replication continues past the (^{6}O-MG) without cell cycle arrest or apoptosis. However, there are cell lines that are resistant to cytotoxic effects of TMZ despite expressing low levels of AGT which indicates that other mechanisms for resistance may be involved.

The applicant submitted a literature review showing that metronomic (protracted low-dose) TMZ treatment can inhibit angiogenesis in both chorioallantoic membrane and HUVEC cell based Matrigel assays. Interestingly comparing the pharmacokinetic parameters (total clearance, volume of distribution, and tumour plasma accumulation) between metronomic and conventional TMZ dosing were quite similar consistent with the linear pharmacokinetic properties of TMZ.

Pharmacokinetics

There were no pharmacokinetic study reports submitted as part of the application. A review of the literature was submitted which described the pharmacokinetic aspects of temozolomide.

TMZ is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Preclinical studies of TMZ revealed good bioavailability after oral administration, schedule-dependent anti-tumour activity. TMZ is not directly active but is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species.

Tissue distribution was assessed in rats in two studies. ^{14}C-TMZ was extensively distributed to all tissues including into the brain. Penetration of temozolomide into the CNS studied in rats and rhesus monkeys showed that the levels of drug in the brain and cerebrospinal fluid are approximately 30% to 40% of the plasma concentration. The metabolite MTIC, however, does not effectively penetrate the CNS. Concentrations in brain and testes appeared to be highest at 1 hour postdose then decreased slowly; higher levels of radioactivity remained in the kidneys, liver, large and small intestinal wall, salivary gland and testes.

Metabolic studies performed in mouse, rat, dog and human, showed comparable metabolism across species. Cytochrome P450 enzymes play only a minor role in the metabolism of TMZ and MTIC. Relative to the AUC of TMZ, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered TMZ total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in faeces. The majority of the recovery of radioactivity in urine is as unchanged TMZ (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of TMZ is about 5.5 L/hr/m^2.

Toxicology

A review of the literature was submitted which described the toxicology aspects of temozolomide. There were no toxicology studies submitted as part of the application.

Single dose toxicity studies were performed in mice, rats, and Beagle dogs. The maximum non-lethal dose was 500 mg/m² (oral, i.p.) in mice, 750 (oral) and 1000 mg/m² (i.p.) in rats and 200 (males)-1500 mg/m² (females) in dogs.

Repeated dose toxicity studies in rats and dogs of up to 6-months duration were conducted using dosing regimens consisting of a 5-day treatment period followed by a 23-day period without treatment, referred to as a cycle. In rats, doses of 50 mg/m²/day were generally well tolerated up to 3 cycles and in dogs up to 6 cycles. Non-clinical studies have shown the haematopoietic and lymphoreticular systems, gastrointestinal tract and testes to be the target sites of TMZ. Except for effects on testes, there was a tendency to recovery during the no treatment period. In addition, in rats, toxicity to the mammary gland, the thyroid gland and the ocular system was evident. Retinal degeneration appears only at very high toxic and fatal doses. Neoplastic changes were noted at 125 mg/m²/day in a 6-cycle study and in female rats, tumours were evident at all doses, starting from a cumulative dose of 750 mg/m². In a 3-cycle study, masses were palpable already on day 62 at a dose of 200 mg/m²/day. At lethal doses in the toxicity studies there were signs of potential CNS effects, such as tremors and prostration (in mice), hypoactivity, hunched posture and partial closure of the eyes (mice and rats) and elevated body temperature (dogs). Clinically only nausea and vomiting have been observed as potential CNS effects. No cardiovascular effects have been seen. There were no renal changes attributed to treatment with TMZ.

The results observed in the pharmacological-toxicological studies indicate that rats and dogs are more sensitive to toxic effects of TMZ. The therapeutic dose of 200mg/m^2 used and tolerated in humans is already within the lethal dose range for animals.

Repeat dose toxicity studies show that TMZ has a carcinogenic potential, which could be expected of this kind of compound. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of the first tumours within three months of initiating dosing. With 6 cycles of treatment at 25, 50, and 125 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses (and even after a dose of 200mg/m^2 on 5 consecutive days every 28 days for 3 cycles) and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.

The literature review of reproductive and development toxicity studies of TMZ comprised of a fertility and early embryonic development study in rats (three cycles of dosing for males, two cycles for females), an embryo-foetal development study in rabbits (dosing on gestation Days 8-12), and a study of effects on pre-and post-natal development (including maternal function) in rabbits (two cycles of dosing).

Effects such as increased postimplantation loss and reduced foetal weight were reported in rat and rabbit embryo-foetal developmental studies, at doses lower (150mg/m^2) than the recommended clinical doses. Malformations, including various skeletal anomalies of the head, axial skeleton, tail, and extremities were observed. In the pre- and post-natal development study, decreased survival rate of pups was reported as well as developmental delays at doses ≥75 mg/m^2. While specific studies on excretion of TMZ in milk have not been conducted distribution studies indicate that a possible effect of exposure to TMZ through milk in addition to exposure via the placenta cannot be ruled out. Although no effects on copulation or fertility were evident in the fertility and early embryonic development study in rats, effects on the testis were observed in repeated dose toxicity studies in rats (≥50 mg/m^2) and dogs (≥125 mg/m^2) and no recovery was observed. Thus an effect of TMZ on male fertility cannot be ruled out.

There are no published preclinical studies available in the scientific literature regarding the local tolerance of temozolomide.

Ecotoxicity/Environmental risk assessment
An ERA has not been submitted for this marketing authorisation application.

The applicant has applied for an exemption of the Environmental risk Assessment based on the fact that products containing temozolomide as drug substance have been authorised in the EU for more than 10 years and that the possible risks for environment arising from use, storage and disposal of the medicinal product are covered by the instructions/ measures that are included in Summary of Product Characteristics.

Discussion on Non-Clinical aspects

The non-clinical overview presented by the Applicant provided an adequate overview of the pharmacological, pharmacokinetic and toxicological aspects of temozolomide. There were no major issues raised during the assessment from a non-clinical point of view.

The pharmacology of temozolomide has been widely investigated, as reflected in the review submitted by the Applicant.

The pharmacokinetics of temozolomide seem generally well characterised. The pharmacokinetic profile of temozolomide was investigated in rats, mice, and dogs.

An ERA was not submitted with this marketing authorization application. Its absence is justified since the submission refers to a generic medicinal product with similar chemical structure, formulation, known pharmacological properties and indications for use as the reference product Temodal. Therefore, it is agreed that this additional drug product will not change the overall use pattern of the existing market.

There have been no new findings which require amendments of the safety and efficacy evaluation or changes in SPC and PL.

2.4 Clinical Aspects

Introduction

The applicant has provided an updated review of the clinical use of temozolomide for the proposed indications with 113 publications from 1989 to 2007.

There were no detailed study reports from clinical trials submitted by the applicant. The application was submitted in accordance with Article 10(1) of Directive 2001/83/EC, where the applicant was not required to provide the results of pre-clinical tests and of clinical trials as the medicinal product is a generic of a reference medicinal product which is authorised for 6/10 years in a MS or in the Community.

Bio-equivalence exemption

According to section 5.3 of the guideline "Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, when a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable. Amongst other conditions, the following should be fulfilled

- The qualitative composition of the different strengths is the same;
- The ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar;

Therefore, the strengths of 100, 140 and 180 mg, which are compositionally dose-proportional, were requested to be waived from the 250 mg strength.

According to section 5.1.1 of the bioequivalence guideline, a drug exhibiting high solubility, high permeability and a high dissolution rate for the medicinal product can be exempted from in vivo bioequivalence studies. Since the 5 mg strength is not compositionally proportional to any of the other strengths, a Biopharmaceutics Classification System (BCS) biowaiver was applied for this strength given that absorption in humans is determined to be almost 100 %, primarily to be due to its acid-stability and lipophilic character.

Therefore, the strength of 5mg was requested to be waived from the 250 mg strength.

The bioequivalence study was conducted with the 20 mg and the 250 mg capsules. The 20 mg strength is not compositionally dose-proportional and therefore a bioequivalence study was also performed on that strength.

Clinical studies

To support the application the applicant has submitted one bioequivalence study including both the 250 mg and the 20 mg strength.

The application contains adequate clinical data from the review of the publication literature for the proposed indications:

- treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- treatment of 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.

Pharmacodynamics

A review of the literature was submitted which described the clinical pharmacodynamic aspects of temozolomide.

There were no clinical pharmacodynamic study reports submitted as part of the application.

Pharmacokinetics

A review of the literature was submitted which described the pharmacokinetic aspects of temozolomide. There were no clinical pharmacokinetic study reports submitted as part of the application.

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC).

Absorption
After oral administration to adult patients, temozolomide is rapidly and completely absorbed, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). Administration of temozolomide with food resulted in a 33 % decrease in Cmax and a 9 % decrease in AUC. As it cannot be excluded that the change in Cmax is clinically significant, temozolomide should be administered without food.

Distribution
Temozolomide demonstrates low protein binding (10 % to 20 %). The mean apparent volume of distribution is 0.4 L/kg. PET studies in humans and preclinical data suggest that temozolomide crosses the blood-brain barrier rapidly and is present in the CSF.

Metabolism
Temozolomide is spontaneously hydrolyzed at physiologic pH primarily to the active species 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. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

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

Clinical efficacy and safety

There were no clinical or safety studies submitted as part of the application.

The therapeutic efficacy of temozolomide in treating refractory malignant infiltrative brain turmours has been studied in 942 adult patients in 15 clinical trials and in 230 children and adolescents in 4 clinical trials. The therapeutic efficacy of temozolomide in treating newly diagnosed glioblastomas and gliomas has been studied in 1975 adult patients in 12 clinical trails, in 64 children and adolescents in 2 clinical trials and in 183 elderly patients in 3 clinical trials.

The oral temozolomide dosage regimen used in these trials was mainly 150 or 200 mg/m2/day for 5 consecutive days, repeated every 4 weeks and showed beside an efficient response a good tolerability across the studies and population subgroups. In patients with recurrent brain tumours, a median PFS in the order of 4 to 7 months and a median OS of 7 to 17 months have been reported after temozolomide treatment. Temozolomide treatment in patients with newly diagnosed GBM revealed a median PFS in the order of 4 to 9 months and a median OS of 6 to 19 months respectively. While adult studies with larger cohorts have confirmed a high response to temozolomide for both low-grade and high-grade AA and other gliomas, the overall paediatric data suggested that temozolomide´s activity may be less robust in children.

An EORTC/NCIC trial with 573 patients, performed by Stupp et al. (2005), provided strong support for the use of temozolomide in conjunction with RT in the treatment of newly diagnosed GBM. More than 90 % of patients in both arms completed RT, and 88 % of those in the RT plus temozolomide arm completed in-tended CT. Temozolomide was discontinued in 12 % of patients because of toxicity (5 %), tumour progression (4 %), or other reasons (3 %). Analysis of the data revealed a median survival of 12.1 months for the patients with RT alone and 14.6 months for patients receiving combined therapy ($p < 0.001$). Two-year survival was 10.4 % for patients with RT alone versus a remarkable 26.5 % for patients receiving combined therapy ($p < 0.001$).

In clinical trials, adverse events associated with temozolomide toxicity were graded according to the WHO and to the CTC of the National Cancer Institute. The most common adverse events associated with temozolomide were drug class effects that stem from its cytotoxic mechanism of action. Sporadic cases of serious adverse reactions that might be due to temozolomide have also been published.

Myelosuppression was the major dose-limiting toxicity in patients treated with temozolomide as monotherapy and/or concomitant with RT. It was predictable but not cumulative. The most commonly observed side effects associated with temozolomide standard therapy were mainly mild-to-moderate nausea, vomiting, constipation, anorexia, headache and fatigue.

Tolerance at doses up to 300 mg/m2/day temozolomide was good. Eight case reports of adverse events during oral use of temozolomide have been identified in the literature. These included the development of secondary, or treatment-related, myelodysplasia and acute myelogenous leukaemia, temozolomide-associated pneumonitis, delirium (likely caused by an interaction between temozolomide and the antiepileptic drug Dilantin) as well as one fatal reaction (reactivation of hepatitis B).

- Methods

STUDY DESIGN

The study was a single centre, cross-over, controlled single-dose bioequivalence study conducted on 29 enrolled male and female patients having the indication of treatment with temozolomide, under fasting conditions, continued with an additional one arm clinical efficacy and safety evaluation. The bioequivalence part of the study was conducted in the second cycle of a temozolomide treatment including up to six temozolomide cycles. In order to obtain also efficacy data, the test product was administered in all cycles of the treatment.

The bioequivalence part of the study was performed for two different strengths of temozolomide; Test 1 (Temozolomide 250 mg capsules) versus Reference 1 (Temodal 250 mg capsules) and Test 2 (Temozolomide 20 mg capsules) versus Reference 2 (Temodal 20 mg capsules). Because of the safety profile of temozolomide, the study was performed in patients instead of healthy volunteers. During the whole study period the following concomitant medication was permitted: antiepileptics except for valproic acid, antiemetics, anti cerebral oedema treatment, other treatments e.g. painkillers as prescribed by the clinical investigator in case of adverse events that requires medication.

The administration schedule was as follows:

Cycle 1: Temozolomide as Test 1 (250 mg) or Test 2 (20 mg) or a combination of both were given once daily for five consecutive days. A total dose of 1000 mg/m2 with a tolerance of ± 15% was given in cycle 1.

Cycle 2 (bioequivalence part): The subjects were admitted to the clinical centre in the evening prior to day 1.

Days 1 and 2: On both treatment days, after an overnight fast of at least 10 hours, each subject received one hard capsule of Test 1 (250 mg) or Reference 1 (250 mg).

Days 3 and 4: On both treatment days, after an overnight fast of at least 10 hours, each subject received the same entire doses of Test 2 (20 mg) or Reference 2 (20 mg). The dosage closest possible (due to the tablet size) to the ideal one for each patient was administered. The number of 20 mg capsules administered was different for each patient and varied from 17 to 31 capsules/day.

In all four days with pharmacokinetic profiling, all study products were administered orally with 240 ml of room temperature plain water. Standard light meals were served at 6, 9 and 12 hours post-dosing, respectively, on days 1 to 4 of the second cycle. Free access to water was granted until 2 hours before each drug administration. Blood samples were collected pre-dose and at 10 min, 20 min, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post-dose on days 1 to 4. Blood samples were immediately put on wet ice until centrifuged to separate the plasma. The plasma was put in duplicate empty test tubes (for determination of MTIC and AIC) or tubes containing phosphoric acid (for determination of temozolomide). Plasma samples were stored at -70 ºC pending analysis.

Day 5: The dose was adjusted in order to obtain at least 1000 mg/m2 per cycle with a tolerance of ± 15%, as a multiple of Test 1 and Test 2. No additional blood sampling was performed.

Cycles 3-6: Dosages received by the patients in the following treatment cycles (starting with cycle nr. 3 until the last cycle performed) were to be presented at the end of the entire study, in an addendum to the present report. This addendum was not included in the file, or could at least not be found, by the assessor.

The study was complying with GCP, as claimed by the applicant.

TEST AND REFERENCE PRODUCTS

Test product 1: Temozolomide 250 mg, hard capsules manufactured by Nerviano Medical Sciences S.r.I., Italy, Batch No. N0800062, Manufacturing date: 01/2008 has been compared to Reference product 1: Temodal 250 mg, hard capsules by Schering-Plough Ltd, Batch No. 121660207, Expiry date: 07/2009.

Test product 2: Temozolomide 20 mg, hard capsules manufactured by Nerviano Medical Sciences S.r.I., Italy, Batch No. N0700751, Manufacturing date: 12/2007 has been compared to Reference product 2: Temodal 20 mg, hard capsules by Schering-Plough Ltd, Batch No. 12167002, Expiry date: 07/2009.

POPULATION(S) STUDIED

A total of 29 male (n=18) and female (n=11) patients aged 21-69 years and with a BMI of 21-37 kg/m2 were enrolled in the study. Out of these 27 started and completed the pharmacokinetic determination part of the study (treatment cycle 2, days 1-4). Two patients were withdrawn before the second treatment cycle due to death (No. 18) and due to thrombocytopenia (No. 21).

ANALYTICAL METHODS

Temozolomide in plasma was determined using a validated HPLC-MS/MS method, and an internal standard (IS) in the interval 17-19 Sept 2008; 22 Dec 2008-15 Jan 2009.
All experiments were carried out on acidified plasma in order to avoid hydrolysis of temozolomide. For the same reason, phosphoric acid was added to the study samples immediately after sampling.

Pre-validation:
Sample pre-treatment involved liquid-liquid extraction. Selectivity was shown employing eight independent sources of human plasma. No significant interference at the retention times for temozolomide or IS was observed. Sensitivity at the limit of quantification was shown. Linearity was demonstrated within the calibration range. Satisfactory between- and within-run accuracy and precision was shown for QC-samples at four concentrations. Recovery was found within an acceptable range for both temozolomide and IS. Dilution integrity was demonstrated for an appropriate dilution factor. Stability in plasma was demonstrated for 3 h on crunched ice, for 9 months at -70 ºC, and over three freeze-thaw cycles. The potential interference of the metabolites MTIC and AIC was also tested; no interference was observed.

Within-study validation:
A total of 1728 plasma samples were analysed of which 27 were reanalysed. Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was adequately justified.

PHARMACOKINETIC VARIABLES
The following pharmacokinetic parameters were determined: AUC0-inf, AUC0-t, Cmax, AUC%extra, t½, MRT and Kel. Conventional non-compartmental methods were used to determine the pharmacokinetic parameters.

STATISTICAL METHODS

The effect of sequence, subject (nested in sequence), period (day of treatment) and treatment on temozolomide Cmax and AUC0-t was separately evaluated, on log-transformed data, using the ANOVA latin square 2 treatments worksheet of SAS. Tmax data was compared using the non-parametric Wilcoxon Signed Rank test.

The bioequivalence acceptance interval was set to 80-125% for the primary pharmacokinetic parameters Cmax and AUC0-t.

- Results

The results from the bioequivalence study is found in table 1 (temozolomide 250 mg) and table 2 (temozolomide 20 mg) below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Temozolomide 250 mg; Test 1/Ref 1 (n=27).

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	22850±5857	23520±5733	7063±2688	1.000 (0.333-6.000)
Reference	22722±5349	23323±5282	7258±2121	0.750 (0.167-6.000)
***Ratio (90% CI)**	**99.66 (95.72-103.77)**	**100.21 (97.07-103.45)**	**94.20 (85.44-103.85)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Temozolomide 20 mg; Test 2/Ref 2 (n=27).

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	41044±6295	41714±6361	14113±3017	0.500 (0.167-1.333)
Reference	40061±4977	40640±5081	13807±3531	0.750 (0.333-3.000)
***Ratio (90% CI)**	**101.92 (99.72-104.16)**	**102.11 (99.91-104.36)**	**103.23 (94.44-112.84)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**ln-transformed values*

The extrapolated AUC was less than 20% in all subjects, except for subject No. 24 who had an extrapolated AUC of 20.833% after administration of temozolomide 250 mg.

- Conclusions

Based on the submitted bioequivalence study Temozolomide Teva 20 mg and 250 mg hard capsules are considered bioequivalent with Temodal 20 mg and 250 mg hard capsules.

The results of study TEM-BESD-01-TIE/07 with the 20 mg and 250 mg formulation can be extrapolated to the strengths 100 mg, 140 mg and 180 mg, according to the conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/1401/98, section 5.3.

The strength of 5 mg is considered bioequivalent based on the concept of BCS-based biowaiver according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/1401/98, section 5.1.1.

Additional data

No additional studies were submitted as part of this application.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5 Pharmacovigilance

- **PSUR**

The PSUR submission schedule for Temozolomide Teva should follow the PSUR schedule for the reference medicinal product, Temodal.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system, version 7 dated May 2009 as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The company must ensure that this system is in place and functioning before the product is placed on the market.

- **Risk Management Plan**

No description of Risk Management plan (RMP) has been provided by the Applicant since the application concerns a medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified.

The well established active ingredient has been in use for many years and the safety profile of the products is very well established.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports. Specific risk minimisation activities are not envisaged as the safety aspects of the product are well characterised and therefore a Risk Minimisation plan is not required.

- **User consultation**

The user testing of the package leaflet was performed. The criterion for a successful Readability Test was fulfilled. The user testing of the package leaflet was judged acceptable.

Discussion on Clinical aspects

Temozolomide has a well-recognized efficacy and an acceptable level of safety in the indications claimed for Temozolomide Teva and no additional clinical studies are needed.

The clinical overview provides an adequate summary of the clinical pharmacology, efficacy and safety of temozolomide. There were no clinical study reports submitted as part of this application
To support the application, the Applicant has submitted one single-dose cross-over bioequivalence study with the 20 mg and the 250 mg strength in adult cancer patients under fasting conditions. The study was conducted on day 1-4 of a 5-days treatment cycle with temozolomide (250 mg given on day 1 and 2 and 20 mg given on day 3 and 4). The bioequivalence study in patients is considered acceptable since temozolomide is a cytotoxic substance and not suitable for administration in healthy volunteers. A study under fasting conditions is adequate given that the reference product should be administered without food. Bioequivalence was shown for Cmax, AUC0-t and AUC0-inf for temozolomide using the conventional acceptance criteria of 80-125%.

A biowaiver was requested for the 100 mg, 140 mg and 180 mg strength, which is acceptable from a pharmacokinetic point of view since the pharmacokinetics of temozolomide is linear.
For the 5 mg strength a BCS-based biowaiver was requested. This is considered acceptable from a pharmacokinetic point of view as the absorption of temozolomide is linear and complete.

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The dossier in question refers to a generic product with a well known active substance which has been marketed for many years throughout the EU. The applicant considers no need for additional risk minimisation measures apart from routine pharmacovigilance.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The non-clinical and clinical literature review provides a consistent overview of the pharmacological, pharmacokinetic and toxicological aspects of temozolomide. Therefore, there were no objections to the approval of Temozolomide Teva 5, 20, 100, 140, 180, 250 mg hard capsules from a non-clinical and clinical point of view. Temozolomide Teva hard capsules should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

An exemption for the ERA can be given for this product since this generic application has identical posology to the active substance. The CHMP agrees that no changes in the environmental risks that are not already known for temozolomide are to be anticipated.

An RMP was considered not required as there are no safety concerns requiring additional risk minimisation activities with respect to the reference medicinal product. It was considered that routine pharmacovigilance according to the Detailed Description of Pharmacovigilance System was sufficient for safety monitoring, without the need for additional actions.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information

The application contains adequate quality, non clinical and clinical data. A benefit/risk balance comparable to the reference product can therefore be concluded.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Temozolomide Teva in the treatment of:
adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment,
and 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,
was favourable and therefore recommended the granting of the marketing authorisation.