19 May 2011
EMA/CHMP/197697/2011

Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Temozolomide Sun

International nonproprietary name: temozolomide

Procedure No. EMEA/H/C/002198

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 Sun Pharmaceutical Industries Europe B.V submitted on 29 June 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Temozolomide Sun, through the centralised procedure falling within the scope of the Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2008.

The legal base for this application refers to Article 10 (1) of Directice 2001/83/EC, as amended.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC, as amended.

The applicant applied for the following indication:

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

- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC, as amended.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product Temodal instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is: Temodal

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: **Temodal 5, 20, 100, 140, 180 and 250 mg hard capsules**
- Marketing authorisation holder: **Schering Plough Europe**
- Date of authorisation: **26/01/1999**
- Marketing authorisation granted by: **Community**
- Marketing authorisation number: **EU/1/98/096/001-012**

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
- Product name, strength, pharmaceutical form: **Temodal 5, 20, 100, 140, 180 and 250 mg hard capsules**
- Marketing authorisation holder: **Schering Plough Europe**
- Date of authorisation: **26/01/1999**
- Marketing authorisation granted by: 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 250 mg hard capsules**
- Marketing authorisation holder: **Schering Plough Europe**
- Date of authorisation: **26/01/1999**
- Marketing authorisation granted by Community

Marketing authorisation number(s): **EU/1/98/096/001-012**

- Bioavailability study number(s): **PKD/08/054**

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 Rapporteur appointed by the CHMP was:

Rapporteur: Tomas Salmonson

- The application was received by the Agency on 29 June 2010.
- The procedure started on 21 July 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 October 2010 (Annex 4.1).
- During the meeting on 15-18 November 2010, 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 19 November 2010 (Annex 4.2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 January 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 February 2011 (Annex 4.3).
- During the meeting on 14-17 March 2011, 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 18 March 2011 (Annex 4.4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 March 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 March 2011 (Annex 4.5).
- During the CHMP meeting on 11-14 April 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 4.6).
- The applicant submitted the responses to the CHMP list of outstanding issues on 10 May 2011
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 11 May 2011 (Annex 4.7).
- During the meeting on 16-19 May 2011, 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 Sun on 19 May 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

Temozolomide Sun 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 decarbazine 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 N7 and 6O positions of guanine although methylation at the 3O position also occurs.

Temozolomide Sun is indicated for the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment. Temozolomide Sun 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 Sun 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 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) ≥ 1.5 x 10^9/l
- thrombocyte count ≥ 100 x 10^9/l
- common toxicity criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly.

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 ≥ 1.5 x 10^9/l, and the thrombocyte count is ≥ 100 x 10^9/l. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/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 (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

Temozolomide Sun is presented as hard gelatin capsules containing 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg of temozolomide as active substance. The ingredients of the capsule content are lactose anhydrous, sodium starch glycollate, tartaric acid and stearic acid. The other ingredients of the capsule shell are gelatin, titanium dioxide and sodium laurilsulfate. The finished product is marketed in Type III amber glass bottles with white polypropylene child-resistant closure with desiccant and packed in cartons.

2.2.2. Active Substance

The chemical name of temozolomide is 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. The structure of this active substance is described in figure 1.

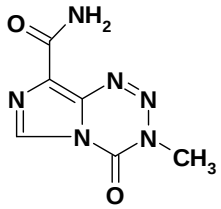

Figure 1: temozolomide

It appears as a white to off white non-hygroscopic powder that is slightly soluble in water and acetonitrile and very slightly soluble in methanol. Temozolomide is achiral but shows polymorphism. One polymorphic form is consistently formed during the active substance production and used in the manufacture of the finished product. There is no Ph. Eur. or USP monograph for temozolomide.

Manufacture

Information about the manufacturing process has been provided using the Active Substance Master File (ASMF) procedure. The manufacturing process of temozolomide is a three step synthesis followed by purification (crystallisation), and adequate controls of critical steps and intermediates are sufficient

to ensure the quality of the active substance. Specifications for starting materials, reagents, and solvents have been provided. The purified active substance is packed under a nitrogen atmosphere in food grade low density transparent polyethylene bags placed in black polyethylene bags. The bags are further packaged in fibre board drums. Statements from the Qualified Persons of the finished product manufacturers confirming that the manufacturing of the active substance is performed in compliance with current EU GMP or ICH Q7A was provided.

The chemical structure of temozolomide has been confirmed by spectroscopy (IR, ^{1}H-NMR, MS, and ^{13}C-NMR). In addition the molecular weight was determined by elemental analysis and the chemical structure was confirmed by X-ray diffraction studies.

Specification

The active substance specification as tested by the finished product manufacturer includes tests for appearance (visual), solubility, identification (IR and X-ray diffraction), clarity, colour index, pH, water content (Ph.Eur.), sulphate ash (Ph.Eur.), heavy metals (Ph.Eur.), impurities (HPLC), residual solvents (GC), assay (HPLC), particle size, bulk density, tapped density, chloride and sulphate. A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH guidelines. In general, the analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been provided and show compliance with the predefined active substance specification.

Stability

The stability results from long-term (5°C ± 3°C) for 5 production scale batches and accelerated studies (25°C/60%RH) for three production scale batches were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: description, identification, (IR and X-ray diffraction), clarity, colour index, pH, water content (Ph.Eur.), impurities (HPLC) and assay (HPLC). The test methods applied are those used for release of the active substance. Based on the results it can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3. Medicinal Product

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate a conventional solid oral dosage form (hard capsule) containing respectively 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg temozolomide per capsule which is bioequivalent to the innovator product, Temodal. In this context, the characteristics of the reference product have been studied in terms of its qualitative and quantitative composition along with its physico-chemical properties. The excipients for this particular formulation were selected carefully. It was noted that the excipients selected for this formulation are commonly used in pharmaceutical formulations. During the pharmaceutical development critical formulation and manufacturing parameters were identified and adjusted. The comparative dissolution profiles were provided. The results demonstrated that the generic batches used for the bioequivalence studies and the EU brand leader batches are similar with respect to dissolution rate.

Adventitious agents

Certificates of suitability have been provided for the gelatine capsule which is of ruminant origin.

Manufacture of the Product

The proposed commercial manufacturing process involves standard technology and it is divided into the following steps: mixing, granulation, wet milling, drying, sifting and dry milling of granules, blending, encapsulation in hard capsules, inspection, metal detection and packaging. Furthermore, the equipment used is commonly available in the pharmaceutical industry. The critical steps in the manufacturing process have been identified and controlled. The manufacturing process has been adequately validated for three production scale batches of each strengths and the results of the manufacturing validation reports were considered satisfactory.

Product Specification

The product specification is standard for hard capsules and contains tests with suitable limits for description, identification (HPLC and TLC), identification of titanium dioxide, dissolution, uniformity of dosage (Ph.Eur), water content, impurities (HPLC), assay (HPLC) and microbial limits test (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Their limits are justified by reference to stability studies. All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for three scale batches of each strength confirm that the hard capsules can be manufactured reproducibly according to the agreed finished product specifications.

Stability of the Product

Three batches of each of hard capsules packed in intended market containers (except for 100 mg and 180 mg, where only one batch has been studied) were placed on stability under ICH conditions 25º C/60% RH for 12 months and 40º C/75% RH for 6 months. Due the number of strengths a bracketing design has been applied by the Applicant. The following parameters were controlled during the stability studies: description, identification (HPLC), uniformity of dosage (Ph.Eur), water content, assay (HPLC), impurities (HPLC) and microbial limits test (Ph.Eur). Photostability testing was conducted on two batches (20 mg) in accordance with the recommendations of ICH guideline Q1B The batches were found to meet the specifications and the finished product does not require any special light protection. Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in

accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated for three production scale batches of each strength at the proposed manufacturing site.

The routine specifications and tests methods proposed for the finished product will adequately control the quality of the finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for finished were adequately established.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished have 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 medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

2.3. Non-Clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature from 30 publications. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

Based on the literature review, Temozolomide is a prodrug, one of a series of imidazotetrazinone derivatives. Temozolomide is a monofunctional alkylating agent that readily crosses the blood-brain barrier, chemically related to dacarbazine and is the 3-methyl derivative of the experimental anticancer drug, mitozolomide. Unlike dacarbazine, temozolomide does not require hepatic metabolism to the intermediate species MTIC but spontaneously hydrolyzes to MTIC above pH 7. MTIC degrades to a highly reactive cation that methylates guanines in DNA at the O6 position, causing base pair mismatch (Denny et al 1994, Newlands et al 1997).

Unsuccessful cycles of mismatch repair eventually lead to breaks and permanent nicks in the daughter strand preventing mitotic division and the cell undergoes apoptosis (D'atri et al 1998, Hirose et al 2001).

***In-vitro* Studies:**

Temozolomide has demonstrated antitumour activity *in vitro* against a variety of malignancies; including glioma, metastatic melanoma, and other difficult-to treat cancers (Sankar et al 1999, van Rijn et al 2000, Raymond et al 1997). Overall the toxicity of temozolomide on a range of human and murine tumour cell-lines showed a wide variation. In human-derived D384 astrocytoma cell lines, temozolomide significantly reduced the surviving fraction of cells when administered once every 24 hours for 4 days compared with a single 24-hour exposure. In addition, a 24-hour exposure to temozolomide 10 µmol/L enhanced the cytotoxicity of fractionally irradiated D384 astrocytoma cells but not U251 glioblastoma cells. A 96-hour exposure to temozolomide 10 µmol/L achieved optimal cytotoxicity of fractionally irradiated D384 cells compared with radiation treatment alone. No such enhancement of cytotoxicity was found for U251 cells (van Rijn et al 2000).

***In-vivo* Studies:**

The pharmacology of temozolomide *in vivo* has been studied in two animal models (rat and mouse) using different mode of administration. Temozolomide (160 mg/kg) as a single subcutaneous injection, increased survival time 1.51-fold in mice with an implanted subcutaneous TLX5 lymphoma compared with untreated controls. A smaller daily dose of Temozolomide over a 5-day period (40 mg/kg/day) increased the survival time in mice 1.81-fold compared with untreated controls (Stevens et al 1987).

Intraperitoneal temozolomide (100 mg/kg qdx5 i.p., n= 13) treatment of high-grade nestin tv-a gliomas provided a 14-day growth delay compared with vehicle controls.

Intraperitoneal temozolomide also showed growth delays against a panel of CNS tumor xenografts in athymic nude mice (Friedman et al 1995). The xenografts, which were implanted either subcutaneously or intracranially, were derived from ependymomas, medullablastomas and childhood and adult high-grade gliomas. A growth delay was defined as the difference between the median time for tumors in treated and control animals to reach five times the volume recorded at treatment initiation. A 5-day, intraperitoneal regimen of temozolomide (411 mg/m2/day) caused growth delays ranging between 40.8 days in adult anaplastic astrocytoma [D-54MG] to >120 days in childhood glioblastoma multiforme [D-456 MG] subcutaneous xenografts. This regimen of temozolomide produced 1.8- to 7.5-fold and 4.7- to 19-fold greater tumor growth delays than intraperitoneal procarbazine (700 mg/m2/day for 5 days) and carmustine (100 mg/m2 for 1 day), respectively. In mice with intracranial xenografts, temozolomide (411 mg/m2/day for 5 days) increased median survival times 1.7- to 13.9-fold.

Some studies showed that temozolomide would have potential synergistic effects with other cytotoxic drugs such as O6-Benzylguanine, radiotherapy, cisplatin, topotecan, 3-aminobenzamine or chloroethylnitrosoureas.

Mechanism of resistance:

Three main DNA repair pathways are responsible for temozolomide resistance. AGT enzyme activity represents the most important mechanism of cell defence. An internal cysteine residue of AGT forms an irreversible covalent bond with the methyl lesion (formed by the methyldiazonium cation) of O6-guanine, a reaction that transfers the offending one-carbon unit from the DNA base at the expense of enzyme inactivation (Pegg et al 1990). Cytotoxicity of temozolomide depends on the equilibrium between rate of O6-methylguanine formation and rate of repair. Intracellular temozolomide

concentrations and AGT levels dictate the equilibrium position. Thus, most cells that have low levels of AGT are sensitive to temozolomide, whereas cells with high AGT levels are often refractory to treatment (Baer et al 1993, Liu et al 1996, Middlemas et al 2000, Tentori et al 1997).

The second mechanism of resistance involves MMR proteins (Liu et al 1996, Middlemas et al 2000, D'atri et al 1998, Taverna et al 2000). The administration of temozolomide by oral gavage (three cycles of 66 mg/kg/day for 5 days repeated every 21 days) produced a >50% decrease in volume in 47% (8 of 17) of paediatric solid tumor xenografts in murine models (Middlemas et al 2000). The dosages used in the murine models and resultant plasma temozolomide concentrations were thought to mimic those recorded in human. A relationship between sensitivity of xenografts to temozolomide and DNA repair proteins was established.

The third mechanism of resistance involves the nucleotide excision repair pathway. Temozolomide-induced N7-methylguanine and N3-methyladenine adducts cause DNA chain termination in the absence of the excision repair protein, poly(ADP)-riobose polymerase (PADPRP) (Liu et al 1999). Temozolomide has been shown to activate the PADPRP (Tisdale et al 1985), pathways and PADPRP inhibitors potentiate temozolomide cytotoxicity (Liu et al 1999, Boulton et al 1995). However, the cytotoxicity of N7-methylguanine and O3-methyladenine lesions are unknown and the excision repair pathway is regarded as being less important than the AGT and MMR pathways (Newlands et al 1997).

2.3.3. 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.

Temozolomide was given to mice, rats and dogs under various forms of administration: orally (PO), intraperitonealy(IP) and intravenously(IV) to determine its pharmacokinetics properties.

The plasma pharmacokinetics of temozolomide following oral and intraperitoneal administration to mice was characterised by rapid absorption phase (the peak plasma concentration being achieved within 30 minutes of administration), and mono-exponential elimination (with an elimination half-life of 1.29 h and 1.13 h following PO and IP administration respectively) (Newlands et al 1997, Stevens et al 1987).

No metabolites were identified in mouse during in vitro study. In an in vivo study, it was found that 39% of temozolomide was excreted unchanged and that a small amount of TMA (temozolomide acid metabolite) was also excreted. No other metabolite was seen.

Temozolomide is rapidly and extensively (> 90%) absorbed and widely distributed following oral and IV administration to rats. The absolute bioavailability of temozolomide is 96-100%. Temozolomide is rapidly converted to MTIC, its reactive metabolite. There are no apparent gender related differences in either temozolomide or MTIC plasma concentration-time profiles. Maximum brain concentrations of temozolomide were observed within 1 h post-dose for both PO and IV route, suggesting rapid penetration of circulating temozolomide into brain tissue (Reyderman et al 2004).

Maximum radioactivity concentrations are observed in kidney, liver, bone marrow, spleen and heart and are higher than those found in plasma. The kidney contains the highest concentrations of radioactivity at 2 h post-dose and the fat contains the lowest. Concentrations at 2 h are 3 and 0.2 times those found in plasma, respectively. The decline of radioactivity is slow in tissue and rapid in plasma. Based on the whole-body autoradiography, the radioactivity in liver, kidney, testis and salivary gland remains prominent at 168 h (1 week) after dosing. The main route of elimination following single IV or PO dose of 14C-drug derived radioactivity was via renal excretion. On average, 81% (range 75-

85%) of the dose were excreted in the urine over 168 h after IV and PO dosing. Comparison of urinary excretion following IV and PO administration demonstrated that 14C-temozolomide was well absorbed (>90%) following oral administration. The initial rate of excretion of drug-derived radioactivity was rapid after either IV or PO administration. Within 24 h post-dose, 75.2% of the IV dose and 66.2% of the oral dose was excreted in the urine and faeces. Excretion of radioactivity in the faeces was low, with approximately 3.5 and 2.8-6.4% of the dose recovered following IV and oral dosing, respectively. The mean cumulative biliary excretion of radioactivity was 1.1 (1.5)% and 1.4(1.6)% of the dose 24 and 48 h after oral (IV) dose, respectively (Reyderman et al 2004).

Following PO dosing in healthy dogs, temozolomide was rapidly and completely absorbed. Its absolute bioavailability ranged from 95-110%. Temozolomide represented about 30% of radiocarbon in plasma by 8 h post-dose.

2.3.4. 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

Acute toxicity studies were conducted in both mice and rats. In single dose studies conducted in mice, calculated LD50 values were 891 (males) and 1072 (females) mg/m2 for oral administration and 1297 (males) and 891 (females) mg/m2 for intraperitoneal administration of temozolomide. In rats, LD50 values were 1937 mg/m2 when temozolomide was given orally and 1414 mg/m2 for intraperitoneal administration. Antemortem observations for both mice and rats included hypoactivity, hunched posture and partial closure of the eyes, tremors, prostration, ataxia, abnormal or few feces, poor appetite, thin appearance, anorexia, swollen heads and dyspnoea. At necropsy, dark-red areas were observed in various organs.

Clinical observations in dogs which received a total dose of 3500 mg/m2 of temozolomide over 6 days included emesis, hypoactivity, ataxia, polypnea, mydriasis and discolored mucoid feces. At necropsy, dark-red areas were observed in the stomach and dark-red to brown material in the gastrointestinal tract. All dogs receiving 200 or 400 mg/m2 survived the 14-day observation period; dogs administered 600, 1000 or 1500 mg/m2 of temozolomide died or were sacrificed in poor condition before the 14-day period was completed. Necropsy observations at doses 1000 mg/m2 included dark areas in the stomach, lymph nodes, cecum, small intestine, heart, urinary bladder and subcutaneous tissue. There was no gross lesion observed at doses <1000 mg/m2 (Product monograph TEMODAL Schering-Plough, January 2009).

Repeat dose toxicity

Repeated dose toxicity studies in rats and dogs were conducted using dosing regimens consisting of a single-cycle up to six-cycles. 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 temozolomide. 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.

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 temozolomide (Product monograph TEMODAL Schering-Plough, January 2009).

Genotoxicity

Temozolomide was found to be mutagenic in two studies: an Ames Assay for bacterial mutagenicity and a human peripheral blood lymphocyte assay. Additional in vitro toxicity studies are not being conducted as both assays were positive for mutagenic potential, and neoplasia has been observed in vivo. Since these findings are consistent with other drugs in this class, it is unlikely that in vivo assays would provide additional information that could impact the clinical use of temozolomide or aid in the assessment of human risk. Therefore, no in vivo mutagenic potential studies were conducted (Product monograph TEMODAL Schering-Plough, January 2009).

Carcinogenicity

Carcinogenicity studies of temozolomide have not been conducted. However, the results of the six-cycle study in rats can be used to evaluate the carcinogenic potential of temozolomide.

Many types of neoplasms were observed in the six-cycle rat study. They included mammary carcinoma, carcinoma *in situ*, keratoacanthoma of the skin and basal cell adenoma.

Mesenchymal neoplasms included fibrosarcoma, malignant schwannoma, endometrial stromal sarcoma, sarcoma, hemangiosarcoma and fibroma. No tumors or indication of preneoplastic changes were observed in the dog studies. Considering that temozolomide is a prodrug of an alkylating agent, MTIC, its carcinogenic potential is not unexpected (Product monograph TEMODAL Schering-Plough, January 2009).

Reproduction Toxicity

In pregnant rats and rabbits, temozolomide did not affect pregnancy maintenance. The results of the multiple-cycle studies indicate testicular toxicity: reduced absolute testes weights occurred in rats at doses of 50 mg/m2 and syncytial cells were observed in the testes of both rats and dogs at doses of 125 mg/m2. These results suggest additional potential reproductive effects including infertility and possibly genetic damage to germ cells.

Testing for reproductive toxicity was limited to dose range finding studies in rats and rabbits.

No significant maternal toxicity was observed and pregnancy rates were not affected in either species. Dosing did not influence implantation rates or lengths of gestation. Resorptions and post implantation loss were increased at the 150 mg/m2/day dose level, compared to 5, 25 and 50 mg/m2/day dose levels. Fetal weights were reduced at 50 (slight) and 150 mg/m2/day. No external variations or malformations were observed in the rat study. In the rabbit study, 18 different types of malformations were observed in the fetuses of rabbits dosed with 125 mg/m2/day. Based on these results, the developmental NOEL is approximately 50 mg/m2/day. These data indicate that temozolomide, like other alkylating agents, has potential to produce embryolethality and malformations in rats and rabbits.

Considering that temozolomide's therapeutic intent is to interfere with mitosis, postnatal growth and development of offspring may be adversely affected by exposure to temozolomide if present in mothers' milk (Product monograph TEMODAL Schering-Plough, January 2009).

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

The preclinical toxicology profile of temozolomide for IV administration is comparable to that of the oral (capsule) formulation and consistent with that of other marketed alkylating anticancer agents. While the IV formulation produced local irritation at the site of injection in both rabbits and rats, the irritation was transient and not associated with lasting tissue damage

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This is justified as the introduction of Temozolomide Sun manufactured by Sun Pharmaceutical Industries Europe B.V is considered unlikely to result in any significant increase in the combined sales volumes for all temozolomide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.6. Discussion and conclusion on Non-Clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of temozolomide are well known. No non-clinical data are submitted with this application. Published literature has been reviewed and is considered of suitable quality.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), justification for not providing new ERA studies is acceptable.

2.4. Clinical Aspects

2.4.1. Introduction

This is an abridged application for tablets containing temozolomide. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of [active substance] based on published literature; this was considered acceptable. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98*) in its current version *is* of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence study was conducted with the 250 mg capsule. The strengths of 20, 100, 140 and 180 mg were requested to be waived from the 250 mg strength.

Since the 5 mg strength is not proportional in terms of composition to any of the other strengths, a Biopharmaceutics Classification System (BCS) biowaiver was requested for this strength. The applicant stated that absorption in human is determined to be almost 100%, primarily to be due to its acid-stability and lipophilic character and hence a complete biowaiver could be justified. The CHMP was not convinced by this theoretical justification. However literature provided in support of the application included a study in which an oral formulation of temozolomide was compared to a 1-hour intravenous infusion resulted in an oral bioavailability of about 100 % (Newlands et al, Br J Cancer 1992;65;287-91). In addition, the excipients included in the Temozolomide Sun formulation are well known and no interaction with the pharmacokinetics of the active substance is expected. Therefore a biowaiver for the 5 mg capsule is considered acceptable.

In conclusion, as all conditions in the document "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" CPMP/EWP/1401/98 are fulfilled, biowaiver for the lower strengths are acceptable.

2.4.2. Pharmacokinetics

Pharmacokinetic studies (PKD-08-054)

Methods

Study design

This was a randomised, multi center, open label, three treatment, three period, six sequence, single dose, crossover, bioequivalence study of the test product Temozolomide 250 mg Capsules of Sun

Pharmaceutical Industries Limited, India and two reference products Temodar (temozolomide) 250 mg capsules from the US market and Temodal (temozolomide) 250 mg capsules from the EU market, in patients with high grade glioma, under fasting conditions.

Temozolomide is usually administered in cycles. Each cycle consists of 5 days of treatment followed by 23 days without treatment. In this study, dosing was done on the first 3 days of a treatment cycle (i.e., Period I, Period II and period III of the study were scheduled on Day 1, Day 2 and Day 3, respectively, of the treatment cycle). After an overnight fast one capsule of 250 mg of either test (A) or reference (B or C) was administered together with 240 ml of water. Fasting continued for at least 4 hours post dose in each period. Blood-samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00 and 12.00 hours post-dose in each period. A washout period of at least 24 hours separated the study periods.

In all the three periods Ondansetron 4 mg I.V. slowly was given 30 minutes (±10 minutes) before drug administration to prevent incidences of emesis. Concomitant medications given during the study were checked for drug – drug interaction by investigator and it was found that concomitant medication had no drug-drug interaction with the study drug.

Test and reference products

Temozolomide Sun 250 mg hard capsules manufactured by Sun Pharmaceutical Industries Europe B.V. (batch No. JK82485A, manufacturing date 11/2008) has been compared to TEMODAL 250 mg hard capsule manufactured by Schering Plough Europe, Belgium (Batch No. 126100106, expiry date: 04/2011.). A batch of the reference product from the US market was also included in this study, it is however not relevant for this application.

Population(s) studied

A total of 20 patients (17 male, 3 female) with high grade glioma were enrolled. The subjects ranged in age from 18 to 72 years and had a mean body weight of 60.7 kg. All 20 subjects completed the study.

Initially 9 subjects (Subject no. 1 -9) were enrolled and dosed in the study before amendment of the protocol. Out of these 9 subjects, only one subject completed all three periods of the study. Since the amendment involved major changes in the study design, samples of these subjects were not considered for analysis to keep harmony of study design amongst subjects used for study evaluation. However safety of these subjects was monitored and reported. Additional subjects were enrolled in order to complete the study with at least 18 evaluable subjects.

Analytical methods

Immediately after centrifugation, plasma samples were divided in two aliquots and stored in tubes containing 25 µl of 2.5 N HCl at -20ºC±5ºC until shipment to the analytical facility. Plasma concentrations of temozolomide were determined with an LC/MS/MS method.

Pre-study validation

The analytical method was validated both in the absence and presence of the co-administered drug ondansetron. Specificity was shown employing six independent sources of human plasma. Sensitivity at the limit of quantification, 0.250 µg/ml, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Linearity was

demonstrated within the calibration range 0.250-20.000 µg/ml. Dilution integrity for a factor of five was demonstrated. Stability in plasma was demonstrated for 20 h at room temperature, for 147 days at – 20 °C and over three freeze-thaw cycles.

Within-study validation
Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was adequately justified. Long-term stability for a period covering the time from first sample collection until last sample analysis (maximum 85 days) was demonstrated.

Pharmacokinetic Variables

Pharmacokinetic variables were calculated using conventional non-compartmental method. The pharmacokinetic variables included C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½ and extrapolated AUC.

Statistical methods

The statistical analysis was performed on log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of temozolomide using ANOVA. The protocol stated that bioequivalence was to be concluded if the 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80-125% for AUC_{0-t} and C_{max}.

Results

The results of the bioequivalence study are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h
Test	21.94 ± 4.72	23.62 ± 4.80	7.66 ± 3.35	1.12 (0.25-8.00)
Reference	20.94 ± 4.50	22.46 ± 4.65	7.44 ± 2.09	1.12 (0.50-2.00)
*Ratio (90% CI)	**105.73 (99.79-112.02)**	**105.32 (99.84-111.11)**	**97.78 (86.31-110.76)**	**-**
$AUC_{0-\infty}$ **area under the plasma concentration-time curve from time zero to infinity** AUC_{0-t} **area under the plasma concentration-time curve from time zero to t hours** C_{max} **maximum plasma concentration** T_{max} **time for maximum concentration**				

*ln-transformed values

No statistically significant sequence or period effect was found in the ANOVA. The extrapolated AUC was less than 20% in all subjects.

Conclusions

Based on the presented bioequivalence study Temozolomide Sun 250 mg hard capsules is considered bioequivalent with Temodal 250 mg hard capsules.

The results of study PKD-08-054 with the 250 mg formulation can be extrapolated to the strengths 20, 100, 140 and 180 mg, according to conditions in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/1401/98, section 5.4

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, section5.1.1.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Additional data

In vitro dissolution data is presented in section 2.3.3 of the CHMP AR.

2.4.5. Post marketing experience

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

2.4.6. Discussion and conclusion on Clinical aspects

Bioequivalence was evaluated in one randomised, multi center, open label, three treatment, three period, six sequence, single dose, crossover, bioequivalence study with the test product Temozolomide 250 mg hard capsules manufactured by Sun Pharmaceutical Industries Limited, India and two reference products; Temodar (temozolomide) 250 mg capsules from the US market and Temodal (temozolomide) 250 mg capsules from the EU market, in 20 patients with high grade glioma, under fasting conditions. Dosing was done on the first 3 days of a treatment cycle (i.e., Period I, Period II and period III of the study were scheduled on Day 1, Day 2 and Day 3, respectively, of the treatment cycle). A 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. Blood-samples were collected pre-dose and up to 12 hours post-dose in each period. A wash-out period of 24 hours separated each period. Temozolomide in plasma was determined with a validated LC/MS/MS method. Bioequivalence was demonstrated for C_{max} and AUC_{0-t} using the conventional acceptance range of 80-125%.

A biowaiver was requested for the 20mg, 100 mg, 140 mg and 180 mg strength, which is acceptable from a pharmacokinetic point of view as the pharmacokinetics of temozolomide is linear.

For the 5 mg strength a BCS-based biowaiver request was submitted as its composition is not proportional to the other strengths. Considering that from a pharmacokinetic point of view as the absorption of temozolomide is linear and complete and that the excipients are well known and no interaction with the pharmacokinetics of the active substance is expected, this is considered acceptable.

2.5. Pharmacovigilance

PSUR

The next data lock point for the reference medicinal product is 12/07/2011.

The PSUR of the reference medicinal product is on a 3-yearly cycle. The PSUR submission schedule should follow the PSUR schedule for the reference product.

Description of the Pharmacovigilance system

The CHMP considers 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.

Risk Management Plan

The application is based on a reference medicinal product for which no safety concerns requiring additional risk minimization activities have been identified.

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.

2.6. User consultation

An acceptable bridging report to the user test of the package leaflet of Temodal has been submitted. The layout discussion, which has been separately held for the package leaflet of Temozolomide Sun, is also found to complete an acceptable user test for the package leaflet of Temozolomide Sun.

2.7. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application concerns a generic version of temozolomide hard capsules. The reference product TEMODAL is indicated in the treatment of

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

- children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy

No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The pivotal basis forms a bioequivalence study with a randomised, multi center, open label, three treatment, three period, six sequence, single dose, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Temozolomide Sun met the protocol-defined criteria for bioequivalence when compared with TEMODAL. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

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.

Recommendation

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