European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT
FOR
Temozolomide Hexal

International Nonproprietary Name:
Temozolomide

Procedure No. EMEA/H/C/1127

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant HEXAL AG submitted on 3 February 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Temozolomide Hexal, 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.

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 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 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, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg hard capsules
- Marketing authorisation holder: Schering Plough Europe
- Date of authorisation: 26 January 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/98/096/001-012

■ *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 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg hard capsules
- Marketing authorisation holder: Schering Plough 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 250 mg hard capsules
- Marketing authorisation holder: Schering Plough Europe
- Date of authorisation: 26 January 1999
- Marketing authorisation granted by: Community
- Community Marketing authorisation number(s): EU/1/98/096/007
- Bioavailability study number(s): Project no: 141-06

The Rapporteur appointed by the CHMP was Tomas 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 3 February 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 15 September 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 October 2009.
- During the CHMP meeting on 16-19 November 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 25 November 2009.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 08 December 2009.
- During the meeting on 14-17 December 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 Hexal on 17 December 2009.
- The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 December 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Temozolomide Hexal 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 Hexal is indicated for the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment. Temozolomide Hexal 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 Hexal 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 Hexal) 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 (see SmPC section 4.2).

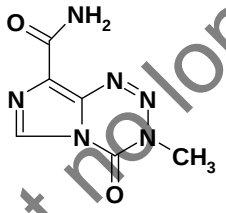
2.2 Quality aspects

Introduction

Temozolomide Hexal is presented as hard gelatin capsules containing temozolomide as active substance. Six strengths have been developed: 5, 20, 100, 140, 180 and 250 mg. Other ingredients are defined in the SPC, section 6.1. The capsules are packed in amber glass bottles (glass type III) or HDPE 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 g/mol.



It appears as a white to light tan /light pink 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

The temozolomide active substance is supplied by one manufacturer. An Active Substance Master File (ASMF) for temozolomide has been submitted. The manufacturing process of temozolomide is a one step synthesis followed by purification. Satisfactory specifications and certificates of analysis are presented for all reagents, raw materials and solvents used in the manufacture of temozolomide and for all critical steps and intermediates used in the manufacture of temozolomide.
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 are provided.

- Specification

The active substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (FTIR, UV, HPLC and XRD), loss on drying (Ph.Eur.), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur.), assay (HPLC), related

substances (HPLC), residual solvents (GC), microbial tests (Ph.Eur.), density (Ph.Eur.), and particle size.
All active substance specifications are considered adequately justified and the analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been presented and show compliance with the predefined active substance specification.

- Stability

Stability results have been provided for three pilot scale batches and three production scale batches; the following parameters have been included in the stability program: description, identification (IR), loss on drying, impurities and assay (HPLC). The batches have been stored for up to 24 months in long term ICH stability conditions, and up to 6 months in accelerated ICH stability conditions. The stability data show compliance with the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The aim of the pharmaceutical development was to formulate a conventional solid oral dosage form (hard capsule) containing respectively 5, 20, 100, 140, 180 and 250 mg temozolomide per capsule and is bioequivalent to the innovator product, Temodal.
The applicant developed a 250 mg, 180 mg, 140 mg, 100 mg and 20 mg capsule which are dose-proportional with regards to the amount of active substance and excipients and fill weight. The lowest capsule strength, 5 mg, is not dose-proportional, but the 5 mg capsule has the same quantitative composition of excipients to those of the 100 mg strength, only using a higher amount of lactose as additional filler. It is considered that the applicant has adequately justified on practical manufacturing grounds that, due to the wide range of strengths, it was not possible to develop a 5mg formulation which is dose-proportional to the 250 mg strength in terms of the excipients and weight.
The excipients used for Temozolomide Hexal are different from 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.

Because temozolomide can be considered as a BCS class I drug substance, and taking into account this medicine's pharmacokinetic properties supported by solubility data provided by the applicant, the particle size is not considered to have any impact on the dissolution properties. It has also been shown that polymorphism has been properly studied and no change in the polymorphic form present in the finished product is expected during shelf life.

Dissolution studies and comparative dissolution profiles with the reference medicinal product have been provided and dissolution characteristics are considered satisfactory.

A bioequivalence study has been submitted for the 250 mg strength.
The absence of bioequivalence studies with the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg capsules 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 the amounts of active substance and excipients is the same for the capsules with strength between 20 mg to 250 mg. The 5 mg strength is not dose proportional but the capsule has the same quantitative composition of excipients to those of the 100 mg strength, only using a higher amount of lactose as additional filler. This was considered acceptable, given that the excipients were not expected to have any influence on the disposition of the drug substance and that rapid dissolution was seen with the drug product. The formulation difference i.e. an increased amount of lactose filler is not expected to have any influence on the disposition of the drug substance.
- the in vitro dissolution profile is similar for the different capsule strengths.

Lactose is derived from animals for which a satisfactory BSE statement has been provided in conformance 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 proving compliance with the current European Pharmaceutical TSE regulations were presented.

- Manufacture of the Product

Temozolomide 5mg/20mg/100mg/140mg/180mg/250mg capsules are manufactured by using conventional manufacturing techniques with dry mixing. The different steps are: sifting, mixing, blending, encapsulation and packaging.

Adequate in-process controls have been set up and a detailed description along with a process flow scheme have been provided. The validation results presented on two industrial batches of each strength show that the capsules can be manufactured reproducibly according to the agreed finished product specification which is suitable for control of this oral preparation.

- Product Specification

The product release and shelf-life specifications include tests for description, identification (HPLC, UV), average net content, uniformity of dosage units, dissolution (UV-VIS spectrophotometer), chromatographic purity, assay (HPLC) and microbial limits test (Ph.Eur).
The analytical methods have been adequately described and validated including:
- the in-house analytical test methods for the description, identification, dissolution, chromatographic purity, assay,
- and the Ph Eur general monographs for the average net content, uniformity of dosage units and microbial limit test.

The comparative impurities profile was performed between Temozolomide Hexal capsules and the reference medicinal product marketed by Schering-Plough Europe, Belgium. Impurity profile was found to be similar as no additional impurities were detected in the generic medicinal product.

Batches analysis data was provided on two production scale batches of each strength, made using different batches of the active substance. Batches met the proposed specification limits. Results showed that capsules can be manufactured reproducibly according to the finished product specifications.

- Stability of the Product

Stability data on the product has been provided for two validation batches per strength of the medicinal product manufactured at the proposed manufacturing site, stored under long term (25°C/60% RH, 6 months) and accelerated (40°C/75% RH,6 months) ICH conditions.

The parameters tested during stability were: description, dissolution, related substance, assay and microbial limit test. Test methods used were the same as those proposed for release testing. The packaging materials used are the same as those proposed for commercial manufacturing.
Temozolomide Hexal capsules have also been placed under stability in polypropylene containers (bulk pack) at 25°C/ 60%RH (6 months). The results showed no significant change in the parameters tested and remained within the proposed specification.

In-use stability study has been performed for temozolomide capsules at 25± 2°C and 60 ± 5% RH for 4 weeks when packed in amber glass bottles and HDPE bottles. Based on the data, it was concluded that the product is chemically and physically stable during in use stability study in both packaging.

Photostability testing was performed in accordance with the recommendations of ICH guideline Q1B on the medicinal product outside and inside the primary package (amber glass bottles and HDPE bottles). No significant change was observed; this shows that the product can be considered stable against light when kept in the original container.

Based on the stability data provided, the proposed shelf life and storage conditions as defined in the SmPC are acceptable.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and medicinal 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. At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the medicinal product.

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 64 publications from 1984 to 2008. 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.

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 O_6 position, causing base pair mismatch. Unsuccessful cycles of mismatch repair eventually lead to breaks and permanent nicks in the daughter strand preventing mitotic division and the cell undergoes apoptosis.

Temozolomide has demonstrated antitumour 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 temozolomide *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 temozolomide 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 temozolomide 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 of 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).

Mechanism of Resistance

The Applicant submitted a literature review showing that metronomic (protracted low-dose) temozolomide 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 temozolomide dosing in xenografted athymic rats treated with either 18-mg/kg/day temozolomide for 5 days or 3.23-mg/kg/day temozolomide for 28 days, were quite similar consistent with the linear pharmacokinetic properties of temozolomide.

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 is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Preclinical studies of temozolomide revealed good bioavailability after oral administration, schedule-dependent antitumour activity. Temozolomide 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-temozolomide 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. Gender differences in tissue concentrations were not identified.

Metabolic studies performed in mouse, rat, dog and human, showed comparable metabolism across species, and showed minimal renal excretion of the parent compound (5-6%), and negligible metabolism of temozolomide to temozolomide acid (TMA) (1 to 2%). Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide 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 temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

Following intravenous or oral administration in rats, temozolomide was primarily eliminated renally (75-85% of the dose) as either unchanged drug, a carboxylic acid analogue, AIC and a highly polar unidentified peak. Biliary excretion was minimal (1.4-1.6%). In mice, the major route of excretion of ^{14}C-TMZ was also renal. A metabolite identified as the 8-carboxylic acid derivative of temozolomide was observed in mice but not in humans.

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 temozolomide. 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 temozolomide.

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

In vitro, temozolomide was found to be mutagenic using the Ames Assay for bacterial mutagenicity and a human peripheral blood lymphocyte assay. *In vivo*, the mutagenic potential of temozolomide was compared to that of cyclophosphamide in mice. The 1-day cyclophosphamide treatment increased the mutational load in bone marrow 2-fold over the control, whereas the temozolomide regimen resulted in a 22-fold increase over control.

Repeat dose toxicity studies show that temozolomide has a carcinogenic potential, which could be expected of this kind of compound. Rats appear to be particularly sensitive to oncogenic effects of temozolomide, 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 temozolomide 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 post-implantation 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 temozolomide in milk have not been conducted distribution studies indicate that a possible effect of exposure to temozolomide 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 temozolomide on male fertility cannot be ruled out.

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

The impurity profile of Temozolomide Hexal 5mg, 20mg, 100mg, 140mg, 180mg, 250mg Capsules manufactured as per their final formula was compared with the impurity profile of reference product Temodal 5mg, 20mg, 100mg, 140mg/180mg/250mg Capsules and was found to be similar as no additional impurities were detected.

Ecotoxicity/Environmental risk assessment

An ERA report was not submitted with this marketing authorization 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.

The impurity profile of the generic formulation has been described as the same of the reference product. All the excipients present in Temozolomide Hexal Capsules are widely used in pharmaceutical products and are well characterised.

An ERA report 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 medicinal 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 SmPC 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 49 publications from 1987 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 20, 100, 140 and 180 mg, which are compositionally dose-proportional, were requested to be waived from the 250 mg strength.

Since the qualitative composition of the 5 mg strength is proportional to all other strengths, the manufacturing process of the 5mg and 250mg capsules is similar, the dissolution profile is similar under identical conditions, and temozolomide demonstrates linear pharmacokinetics with the area under the concentration time curve (AUC) increasing in proportion to the dose, the 5mg strength was also requested to be waived from the 250mg strength.

A biowaver was supported for the 5 mg on the basis of bridging from the 100 mg formulation, on the ground that these formulations are essentially the same except from the amount of lactose filler, which is not expected to have any influence on the absorption and disposition of the drug substance.
For further information see the Quality part of this report.

Clinical studies

To support the application the applicant has submitted one bioequivalence study including the 250 mg strength (Study 141-06).

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 32 % 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 ^{14}C elimination is renal.
Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4- carboxamide (AIC) or unidentified polar metabolites. Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

Clinical efficacy and safety

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

Based on the literature review, the therapeutic efficacy of temozolomide in treating refractory malignant infiltrative brain tumours 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/m^2/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/m^2/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).

Single-dose cross-over bioequivalence study with the 250 mg capsule in adult, cancer patients under fasting conditions

- Methods

STUDY DESIGN (141-06)

The study was an open label, multicentre, randomised, two-period, two-treatment, two sequence, single dose, crossover and comparative oral bioavailability study undertaken of two formulations of Temozolomide Capsules 250 mg in adult, male and/or female human patients under fasting conditions.

The study was conducted on day 1 and day 2 of a 5-days treatment cycle with temozolomide. Some patients were already on temozolomide treatment, and for these patients the study drug was administered after a drug free interval of 23 days.

After an overnight fast one capsule containing 250 mg of temozolomide was administered together with 240 ml of water. Water was not allowed for one hour before drug administration until one hour post-dose (except for the 240 ml). Fasting was continued for two hours post-dose when a standardised lunch was served. Blood samples were collected pre-dose and at 0.16, 0.25, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 10.0 hours post-dose in each period. The two periods were separated by a wash-out period of about 24-hours.

Antiemetics, antacids, NSAIDs, antibiotics, anticonvulsants and corticosteriods were to be allowed during the course of the trial. Co-adminstration of sodium valproate was not to be allowed as administration of valproic acid decreases the clearance of temozolomide. If drug therapy other than that specified in the protocol was required prior to or during the study, decisions was to be taken by the investigator to continue or discontinue the patient based on the pharmacology and pharmacokinetics of the non-study medication, the likelihood of an interaction and the time and duration of administration of the non-study drug.

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

TEST AND REFERENCE PRODUCTS

Test product: Temozolomide 250 mg capsules manufactured by Intas Pharmaceutical Ltd, India, Batch No. H3026, Expiry date: April 2009.has been compared to Reference product 1: Temodal 250 mg, hard capsules by Schering-Plough Ltd, Batch No. 115637501, Expiry date: April 2008.

POPULATION(S) STUDIED

A total of 37 adult male (n=24) and female (n=13) patients aged 18-65 years with a BMI within the range 17-28 kg/m^2 were enrolled and dosed in the study (1-15 patients per study site). Patients with newly diagnosed glioblastoma multiforme on monotherapy phase with temozolomide and patients of recurrent or progressive malignant glioma, previously treated with chemotherapy were included.

A total of 34 patients completed both periods of the study. Subject No. B04 was withdrawn due to non-compliance, subject No. B07 was withdrawn due to emesis after dose administration in period II and subject No. B12 discontinued on his own record.

ANALYTICAL METHODS

Temozolomide and MTIC in plasma were determined using a validated LC-MS/MS method at Lambda Therapeutic Research Ltd between 9 July 2007 and 22 March 2008 for temozolomide and between 13 July 2007 and 26 March 2008 for MTIC.

According to the protocol, immediately after sampling the study samples were to be placed on ice and centrifuged at 4 ºC before freezing and tranportation to the analytical faciclity. After thawing, 50 µl of 5% formic acid was added whereafter the samples were further processed and analysed.

Temozolomide pre-validation data:
Sample pre-treatment involved liquid-liquid extraction. 5-hydroxymethyl tolterodine was used as internal standard (IS). 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, 99.224 ng/ml was shown. Linearity was demonstrated within the calibration range 99.224-20036.697 ng/ml. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Satisfactory accuracy and precision in presence of co-administered drugs (aspirin, paracetamol, ibuprofen and ranitidine) was also shown for low QC samples. Absolute recovery was in the range 61-63% for temozolomide and about 49% for IS. Dilution integrity was demonstrated for a dilution factor of 10. Stability in plasma was demonstrated for 73 h in autosampler, for 6 h at 4 ºC on bench top, for 45 days at -65±10 ºC and over three freeze-thaw cycles.

MTIC pre-validation data:
Sample pre-treatment involved a protein precipitation method. Sumatriptane was used as IS. Selectivity was shown employing eight independent sources of human plasma. No significant interference at the retention times for MTIC or IS was observed. Sensitivity at the limit of quantification, 2.996 ng/ml was shown. Linearity was demonstrated within the calibration range 2.996-605.668 ng/ml. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Satisfactory accuracy and precision in presence of co-administered drugs (aspirin, paracetamol, ibuprofen and ranitidine) was also shown for low QC samples. Absolute recovery was in the range 71-84% for MTIC and about 76% for IS. Dilution integrity was demonstrated for a dilution factor of 10. Stability in plasma was demonstrated for 8 h in autosampler, for 2 h at 4 ºC on bench top, for 63 days at -65±10 ºC 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.

PHARMACOKINETIC VARIABLES

The primary pharmacokinetic parameters were Cmax, AUC0-t and AUC0-inf. Secondary parameters were Tmax, λ, t½ and residual area. Conventional non-compartmental methods were used to determine the pharmacokinetic parametrs.

STATISTICAL METHODS

Analysis of variance (ANOVA) was carried out by employing PROC MIXED of SAS Release 9.1.3 (SAS Institute Inc., USA) for the un-transformed and ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for temozolomide and MTIC.

The ANOVA model included Sequence, Formulation and Period as fixed effects and Patient (Sequence) as a random effect. Sequence effect was tested using Patient (Sequence) as error term. The ANOVA model was also planned to include terms for Centre, Sequence, Sequence

by Centre, Patient (Within Sequence by centre), Treatment, Treatment by Centre and Period (Within Centre). However, the Centre effect was removed from the ANOVA model as there were two centres having only one patient.

Two one-sided tests for bioequivalence and 90% confidence interval for both the un-transformed and ln-transformed ratios of the least squares mean between the formulations were calculated for temozolomide and MTIC. Ratio of least squares means of test and reference formulation was computed for un-transformed and ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for temozolomide and MTIC.

Bioequivalence was concluded if the 90% confidence interval for Cmax, AUC0-t and AUC0-inf for temozolomide and MTIC fell within the acceptance range of 80-125%.

- Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Temozolomide (n=34).

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
• **Test**	29579.442 ± 6156.2288	31148.510 ± 6197.1265	9469.983 ± 3869.4064	2.000 (0.330-6.000)
• **Reference**	28910.431 ± 6660.4445	29881.148 ± 6823.5253	10227.851 ± 4359.4082	1.125 (0.250-6.000)
• ***Ratio (90% CI)**	**103.7 (99.81-107.71)**	**105.7 (101.53-110.03)**	**96.1 (85.71-107.67)**	**-**

- 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*

A statistical significant period effect was found for ln-transformed Cmax, for un-transformed and ln-transformed AUC0-t and for un-transformed AUC0-inf.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for MTIC (n=34).

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h
• **Test**	1723.862 ± 728.1800	1812.577 ± 742.9825	598.965 ± 402.8656	2.000 (0.250-6.000)
• **Reference**	1659.682 ± 623.9332	1725.907 ± 663.2465	660.066 ± 386.7845	1.250 (0.250-4.000)
• ***Ratio (90% CI)**	**103.5 (99.01-108.41)**	**105.0 (100.40-109.73)**	**92.5 (80.88-105.81)**	**-**

- 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 10% in all subjects, except for No. I01 who had an extrapolated AUC for both temozolomide and MTIC of about 14% and 26% after administration of the reference and test formulation respectively.

- Conclusions

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

The results of study 141-06 with the 250 mg formulation can be extrapolated to the strengths of 20 mg, 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.

A biowaver was also granted for the 5 mg on the basis of bridging from the 100 mg formulation, on the ground that these formulations are essentially the same except from the amount of lactose filler.

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 Hexal should follow the PSUR schedule for the reference medicinal product, Temodal.

- **Description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system, Edition 9.0 dated 01 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 Hexal 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 an open label, multicentre, randomised, two period, two-treatment, two-sequence, single dose, crossover and comparative oral bioavailability study in adult, male/female human cancer patients under fasting conditions, with the 250mg capsule.

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 20mg, 100 mg, 140 mg and 180 mg strength, which is acceptable from a pharmacokinetic point of view since the pharmacokinetics of temozolomide is linear.

A biowaiver was requested for the 5 mg strength, which is not dose-proportional to the 250 mg strength. However, the formulations were considered sufficiently similar to support a biowaver taking into account the drug substance is a BCS class I drug substance. The biowaver was also considered acceptable for the 5 mg strength on the basis of bridging from the 100 mg formulation, on the ground that these formulations are essentially the same except from the amount of lactose filler, which is not expected to have any influence on the absorption and disposition of the drug substance.

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 Hexal 5, 20, 100, 140, 180, 250 mg hard capsules from a non-clinical and clinical point of view. Temozolomide Hexal 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 originator's Medicinal Product. 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 Hexal 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.