CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Temozolomide Glenmark 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard Glenmark Pharmaceuticals s.r.o., Czech Republic

temozolomide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2489/001-006/DC
Registration number in the Netherlands: RVG 110831, 110834, 110836, 110838, 110839, 110840

31 October 2013

Pharmacotherapeutic group:	antineoplastic and immunomodulating agents; other alkylating agents
ATC code:	L01AX03
Route of administration:	oral
Therapeutic 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.
Prescription status:	prescription only
Date of authorisation in NL:	7 October 2013
Concerned Member States:	Decentralised procedure with BG, CZ, HU, PL, RO, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Temozolomide Glenmark 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard from Glenmark Pharmaceuticals s.r.o. The date of authorisation was on 7 October 2013 in the Netherlands.

The product is indicated for the treatment of:

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

A comprehensive description of the indications and posology is given in the SPC.

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules which have been registered via a centralized procedure (EU/1/98/096/001-012) by Schering-Plough N.V./S.A. since 26 January 1999. Further information can be found in the EPAR of Temodal (http://www.ema.europa.eu).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Temodal 250 mg capsules, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is temozolomide, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.*). It is a white to light tan/light pink coloured powder, which is soluble in methanol and is slightly soluble in water and acidic aqueous solution. Temozolomide is known to exist in several polymorphic forms. Form III is used.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of temozolomide consists of two steps, followed by a purification step. Acceptable specifications have been adopted for all reagents and solvents.

Quality control of drug substance
The MAH has adopted the specifications of the drug substance manufacturer, with the addition of a limit for particle size. In-house methods and specifications are described for the non-compendial tests. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four production-scale batches.

Stability of drug substance
Stability data on the active substance has been provided for 4 full-scale batches stored at 40°C/75% RH (6 months) and 25°C/60%RH (24 months). No changes or trends were seen at both storage conditions. In view of the stability data, the claimed retest period of 30 months when stored between 2 - 8°C is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The 5 mg product is a hard gelatin capsule size 0 (green opaque cap/white opaque body) with 5 printed in black ink on the body.
The 20 mg product is a hard gelatin capsule size 0 (orange opaque cap /white opaque body) with 20 printed in black ink on the body.
The 100 mg product hard gelatin capsule size 0 (purple opaque cap /white opaque body) with 100 printed in black ink on the body.
The 140 mg product is a hard gelatin capsule size 0 (blue opaque cap /white opaque body) with 140 printed in black ink on the body
The 180 mg is a hard gelatin capsule size 0 (chocolate brown opaque cap /white opaque body) with 180 printed in black ink on the body.

The 250 mg is a hard gelatin capsule size 0 (white opaque cap /white opaque body) with 250 printed in black ink on the body.

The capsules are packed in white opaque High Density Polyethylene bottles with polypropylene push lock assembly closure, with polyester coil and dessicant and sachets composed of paper on linear low density polyethylene (outermost layer), aluminium and ethylene acrylic acid co-polymer (innermost layer).

The excipients are: lactose anhydrate, croscarmellose sodium, colloidal silicon dioxide, tartaric acid, and stearic acid. The capsule shells contain gelatine and titanium dioxide, and different colorants per strength. The capsules are imprinted with black printing ink.

The 100, 140 and 180 mg temozolomide capsules are dose-proportional to the 250 mg strength. The 5 and 20 mg formulations are identical to the 250 mg strength, except that the reduced quantity of drug substance is substituted with the filler lactose anhydrate.

Pharmaceutical development

The primary goals of the development were to formulate a bioequivalent product that could be easily manufactured, that would be stable in the marketed configurations and was essentially similar to the originator product, marketed as Temodal.
The composition of the capsules used in the bioequivalence study is identical to the proposed commercial composition. The bioequivalence study was performed with the 250 mg capsule only. For the other strengths a biowaiver of strengths is applied. This biowiaver of strengths is adequately supported by a comparison of dissolution characteristics between a 250 mg batch and the other strengths at three pH values, and additional data on solubility and permeability that adequately demonstrate that the BCS-Based Biowaiver criteria are fulfilled in order to support the waiver of bioequivalence studies for the 5 mg and 20 mg strength.

Manufacturing process

The drug substance and excipients are sieved and dry mixed. The powder mass is filled into the capsule shells. The capsules are then packed into their respective packages. The manufacturing process is seen as a standard process and has been satisfactorily described. The manufacturing process has been adequately validated on 13 full-scale batches.

Control of excipients

The excipients comply with the Ph.Eur. and the specifications are acceptable. For the capsule shells in-house specifications are included. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, uniformity of dosage units, dissolution, assay, related substances and microbiological quality. The release requirements are acceptable. The end of shelf-life limits are identical to the release limits except for the 5 and 20 mg strengths where the release limit for one impurity is tighter at release. Batch analysis data have been provided for four batches of each strength and five batches of the 5 mg strength. Compliance with the proposed release requirements is demonstrated.

Stability of drug product

Stability data have been provided for 4 batches of each strengths, two packaged in the HDPE container and two in an Aluminium sachet, for the latter only data for 12 months of storage is available. The drug product packed in the HDPE bottles has been stored at long-term conditions (25°C/60%RH) for up to 24 months (12 batches), intermediate conditions (30°C/65%RH) for up to 12 months (12 batches) and at accelerated conditions (40°C/75%RH) for up to 6 months (12 batches). The drug product in sachets has been stored at long-term conditions (25°C/60%RH) for up to 12 months (12 batches), intermediate conditions (30°C/65%RH) for up to 12 months (8 batches) and at accelerated conditions (40°C/75%RH) for between 1 and 6 months (12 batches). The capsules were shown to be photostable. Based on the stability data provided, following shelf-lives can be granted:

- 24 months when stored below 30°C in the HDPE bottle.

- For the 5 mg and 20 mg strength: 12 months when stored below 25°C in the sachet.
- For the other strengths: 18 months when stored below 30°C in the sachet.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Of the excipients, only lactose monohydrate and hard gelatin capsules are of animal origin. For both the lactose monohydrate and the hard gelatin capsule, documentation has been provided that these materials are in full compliance with the EU regulatory TSE requirements.

II.2 Non-clinical aspects

This product is a generic formulation of Temodal, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of temozolomide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Temozolomide is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Temozolomide Glenmark 250 mg (Glenmark Pharmaceuticals s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Temodal 250 mg capsules (Schering-Plough, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study is justified, as it has been authorised through a centralised procedure, and is therefore identical across the EEA.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in patients with high grade glioma/astrocytoma under fasting conditions. There were 28 subjects, 13 males and 15 female patients aged 22-68 years.
Patients with high grade glioma/astrocytoma who can be administered a 250 mg dose of temozolomide in day 1 and 2 of the first cycle of treatment were included. From days 3 to 5, an approved dose of 250 mg temozolomide marketed in the country of testing was administered once daily for 3 days. From the second cycle onwards, the same dose of temozolomide was given at a dose of 175 mg/m^2 of body surface area for the first five days of every 4 weeks (28 days per cycle) till patient completes all the six cycles of therapy or the disease progression whichever is earlier.
The drug was administered with 240 ml of water, after an overnight fast of 10 hours. A washout period of 1 day was kept between dosing periods.

During the pharmacokinetic determination days (days 1 and 2 of Cycle 1) venous blood samples were taken at the following time points: pre-dose, at 0.083, 0.167, 0.25, 0.33, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post dose.

Temozolomide is a cytostatic agent, and for this reason no routine healthy volunteer bioequivalence study can be conducted. In this study glioma/astrocytoma patients received the test and reference drug at day 1 and 2 of treatment cycle 1. This setup is considered acceptable.
In fact, in this study there is a washout period of less than one day, since equal doses were administered at subsequent days. However, considering the very short $t_{1/2}$ of temozolomide (approximately 2-3 hours in this study, this is considered acceptable. This is supported by the fact that no carry-over is detected in any patient. In conclusion, the study design is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 28 patients completed the study and were evaluable regarding pharmacokinetic profiling.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of temozolomide under fasted conditions.

Treatment N=28	**AUC_{0-t}** microg.h/ml	**$AUC_{0-\infty}$** microg.h/ml	**C_{max}** microg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	17.2 ± 7.0	18.4 ± 7.4	5.9 ± 2.5	1.25 (0.33-2.0)	1.7 ± 0.2
Reference	18.0 ± 7.8	19.1 ± 7.9	6.5 ± 3.0	1.0 (0.33-2.0)	1.7 ± 0.2
***Ratio (90% CI)**	0.96 (0.91-1.02)	0.97 (0.91-1.02)	0.94 (0.86-1.01)	--	--
CV (%)	12.9	12.2	17.7	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of temozolomide under fasted conditions, it can be concluded that Temozolomide Glenmark 250 mg and Temodal 250 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
There were no serious adverse events related to the investigational drug in the study. Nausea was reported by 10.7% of the patients receiving the test formulation, whereas 3.6% of the patients receiving the reference formulation vomited, and 7.1% reported nausea. 3.6% of the patients receiving the test formulation developed rashes.

The SPC states that temozolomide should be taken without reference to food intake. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to different strengths
A biowaiver has been granted for the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strengths. The following conditions are fulfiled:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the 100, 140, 180 and 250 mg strength are dose-proportional.
- the 5 and 20 mg formulations are identical to the temozolomide 250 mg biobatch except that the reduced quantity of drug substance is substituted with filler and the amount of the active substance(s) is less than 5 % of the tablet core weight,.
- appropriate in vitro dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.
- temozolomide demonstrates linear pharmacokinetics with the area under the concentration time curve (AUC) increasing in proportion to the dose.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Temozolomide was first approved in 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of temozolomide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Temodal capsules (EU/1/98/096/001-012).

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Both the first and the second test round met the success criteria of 90 % of the subjects being able to locate the requested information, and of those, 90 % being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (content, language and layout) was mostly positive. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Temozolomide Glenmark 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Temodal hard capsules. Temodal is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Temozolomide Glenmark 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 24 January 2013. Temozolomide Glenmark 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules, hard were authorised in the Netherlands on 7 October 2013.

The date for the first renewal will be: 17 September 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform validation of the manufacturing process of the drug substance on a third full-scale batch of the highest strength (250 mg).
- The MAH will continue stability testing on full-scale production batches. Ongoing stability studies will be conducted according to the requirements of Good Manufacturing Practice.
- The MAH committed to place an additional bulk batch of 5 and 100 mg strengths on stability at 25°C/60% RH and 30°C/65% RH.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached