

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Temozolomide Fair-Med 5mg, 20 mg, 100 mg, 140 mg, 180 mg
and 250 mg, capsules hard
Fair-Med Healthcare GmbH, Germany**

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/2372/001-006/DC
Registration number in the Netherlands: RVG 109653 - 109658**

4 October 2013

Pharmacotherapeutic group:	antineoplastic agents and immunomodulating agents; other alkylating agents
ATC code:	L01AX03
Route of administration:	oral
Therapeutic indication:	Adults only - newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment; children from the age of three years, adolescents and adult patients - malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy
Prescription status:	prescription only
Date of first authorisation in NL:	18 July 2013
Concerned Member States:	Decentralised procedure with CY, DE, DK, IE, MT and PL
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 Fair-Med 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules hard, from Fair-Med Healthcare GmbH. The date of authorisation was on 18 July 2013 in the Netherlands.

The product is indicated for:

- 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, 20, 100, 140, 180 and 250 mg capsules (EU License EU/1/98/096) which have been registered through a centralised procedure by Schering Plough Europe since 1999..

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 <member state>. 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.

Scientific advice has been given to the MAH on the question if principle biowaiver was applicable to the product.

No paediatric development programme has been submitted. This is not required for generic medicinal products.

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 which is not described in the Ph.Eur.* or any other pharmacopoeia. Temozolomide is a white to light tan/light pink coloured powder which is slightly soluble in dimethyl sulphoxide, acetic acid and water. The active substance is achiral, but shows polymorphism. One polymorphic form III is used in the manufacture of the product.

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 presented in the ASMF of the supplier, 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 by 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

Temozolomide Fair-Med 5 mg are hard gelatin capsules size 0 (green opaque cap/white opaque body) with 5 printed in black ink on the body.

Temozolomide Fair-Med 20 mg are hard gelatin capsules size 0 (orange opaque cap/white opaque body) with 20 printed in black ink on the body.

Temozolomide Fair-Med 100 mg are hard gelatin capsules size 0 (purple opaque cap/white opaque body) with 100 printed in black ink on the body.

Temozolomide Fair-Med 140 mg are hard gelatin capsules size 0 (blue opaque cap/white opaque body) with 140 printed in black on the body.

Temozolomide Fair-Med 180 mg are hard gelatin capsules size 0 (chocolate brown opaque cap/white opaque body) with 180 printed in black ink on the body.

Temozolomide Fair-Med 250 mg are hard gelatin capsules size 0 (white opaque cap/white opaque body) with 250 printed in black ink on the body.

The hard capsules are packed in white opaque High Density Polyethylene Bottles with Polypropylene push lock assembly closure, with polyester coil and dessicant containing 5 capsules, or in sachets composed of paper on linear low density polyethylene (outermost layer), aluminium and ethylene acrylic acid co-polymer (innermost layer). Each sachet contains 1 hard capsule and is dispensed in a cardboard carton, the carton contains 5 or 20 hard capsules individually sealed in sachets.

The excipients are:

Capsule content: lactose anhydrous, silica colloidal anhydrous, sodium starch glycollate (Type A), tartaric acid, stearic acid.

Capsule shell:

5 mg: gelatin, titanium dioxide (E 171), yellow iron oxide (E 172), indigotine FD & C Blue 2 (E132)

20 mg: gelatin, titanium dioxide (E 171), red iron oxide (E 172), yellow iron oxide (E 172)

100 mg: gelatin, titanium dioxide (E 171), red iron oxide (E172), indigotine FD & C Blue 2 (E132)

140 mg: gelatin, titanium dioxide (E 171), indigotine FD&C blue 2 (E 132)

180 mg: gelatin, titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), black iron oxide (E 172)

250 mg: gelatin, titanium dioxide (E 171)

Printing ink black: shellac, propylene glycol, purified water, sodium ammonia solution, potassium hydroxide, black iron oxide (E 172).

All excipients comply with the Ph.Eur., except for the dyes in the printing ink. The excipients and packaging are usual for this type of dosage form.

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

Pharmaceutical development

The primary goals of the development was 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 by Schering-Plough Ltd. 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 requested. This biowaiver is supported by a comparison of dissolution characteristics between test and reference product.

Manufacturing process

Lactose anhydrous, colloidal silicon dioxide, tartaric acid, stearic acid and the drug substance are sieved and dry mixed. The powder mass is filled into the capsule shells. The capsules are packed into their respective containers. 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. The analytical methods are adequately described.

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. Batch analysis data have been provided for three batches of each strength. Compliance with the proposed release requirements is demonstrated.

Stability of drug product

Stability data have been provided for 4 batches of each strength, two packaged in the HDPE container and two in an Aluminium pouch, for the latter only data for 6 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 (10 batches), intermediate conditions (30°C/65%RH) for up to 12 months (9 batches) and at accelerated conditions (40°C/75%RH) for up to 6 months (13 batches). Results of a photostability study in accordance with the Note for Guidance on the photostability testing of new Active Substances and Medicinal Products demonstrate that the drug product is 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: 6 months when stored below 25°C in the sachet
- For the other strengths: 9 months when stored below 30°C in the sachet.

Bulk stability was only provided for one batch of the 5 mg and one batch of the 100 mg strength for a period of 6 months. An additional batch of both strengths will be placed on stability post approval.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate complies with the Note for Guidance EMEA/410/01 rev.2, so a theoretical risk of transmitting TSE can be excluded. For the gelatine used in the capsule shells EDQM Certificates of Suitability with respect to TSE safety have been provided.

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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Temozolomide Fair-Med 250 mg, capsules hard is compared with the pharmacokinetic profile of the reference product Temodal 250 mg hard capsules.

The choice of the reference product in the bioequivalence study has been justified since Temodal tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A randomised, single centre, open label, two treatment, single dose, cross-over bioequivalence study was carried out under fasted conditions in 28 male (13) and female (15) glioma/astrocytoma patients, aged 22-68 years. 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.

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 was administered once daily for 3 days. From the second cycle onwards, the same dose of temozolomide was be given at the dose of 175 mg/m² of body surface area for 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 orally administered with 240 ml water after an overnight fast of 10 hours.

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.

Blood samples were collected on days 1 and 2 of Cycle 1 at the following time points: predose and 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 after administration of the products.

The study design is acceptable. A GCP statement has been provided.

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 $\pm$ SD, t_{max} (median, range)) of temozolomide under fasted conditions.

Treatment N=28	AUC _{0-t} microg.h/ml	AUC _{0-∞} microg.h/ml	C _{max} microg/ml	t _{max} h	t _{1/2} h
Test	17.2 $\pm$ 7.0	18.4 $\pm$ 7.4	5.9 $\pm$ 2.5	1.25 (0.33-2.0)	1.7 $\pm$ 0.2
Reference	18.0 $\pm$ 7.8	19.1 $\pm$ 7.9	6.5 $\pm$ 3.0	1.0 (0.33-2.0)	1.7 $\pm$ 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-∞} 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					

**In-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 Nogron 250 mg, capsules hard and the Temodal 250 mg hard capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Temozolomide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of temozolomide. 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.

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.

Biowaiver

A biowaiver was requested for the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strength. The 100 mg, 140 mg and 180 mg strengths are dose-proportional to the 250 mg. Since the other requirements as stated in the *NfG on the investigation of bioavailability and bioequivalence* are also fulfilled, data obtained for the 250 mg strength can be extrapolated to these strengths.

The 5 mg and 20 mg are not dose proportional and formally, data obtained for the 250 mg strength can normally not be extrapolated to the 5 mg and 20 mg strength. However, the 5 and 20 mg pilot formulations are identical to the temozolomide 250 mg biobatch except that the reduced quantity of drug substance is substituted with filler. The excipients are well known and no interaction with the pharmacokinetics of the active substance is expected.

Considering the fact that temozolomide is a BCS (Biopharmaceuticals Classification System) class I drug, absorption is not expected to be affected by the quantitative difference in excipients, and therefore a waiver can be granted for the 5 mg and 20 mg strength as well.

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 marketed by Schering Plough Europe.

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 readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Temozolomide Fair-Med 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 5mg, 20mg, 100mg, 140mg, 180mg and 250mg 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 and are in agreement with other temozolomide containing products.

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 Fair-Med with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 26 September 2012. Temozolomide Fair-Med 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, capsules hard is authorised in the Netherlands on 18 July 2013.

The date for the first renewal will be: 26 September 2017.

There were no post-approval commitments made during the procedure.

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 _{1/2}	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