CBG MEB

Public Assessment Report

Scientific discussion

Temozolomide Hetero 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules

(temozolomide)

NL/H/3568/001-006/DC

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This module reflects the scientific discussion for the approval of Temozolomide Hetero 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules. The procedure was finalised on 26 October 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Temozolomide Hetero 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules from Hetero Europe S.L.

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 SmPC.

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 has been registered by Schering Plough Europe since 26 January 1999 through a centralised procedure (EMEA/H/C/000229).

The concerned member state (CMS) involved in this procedure is Malta.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Temozolomide Hetero is a hard gelatin capsule filled with off white to pale pink granular powder:
- Temozolomide Hetero 5 mg is a size '3' capsule (opaque green cap/white body) with '13' printed on the cap and 'H' on the body. Each capsule contains 5 mg temozolomide.
- Temozolomide Hetero 20 mg is a size '4' capsule (opaque yellow cap/white body) with '14' printed on the cap and 'H' on the body. Each capsule contains 20 mg temozolomide.
- Temozolomide Hetero 100 mg is a size '1' capsule (opaque pink cap/white body) with '15' printed on the cap and 'H' on the body. Each capsule contains 100 mg temozolomide.
- Temozolomide Hetero 140 mg is a size '0' capsule (opaque blue cap/white body) with '16' printed on the cap and 'H' on the body. Each capsule contains 140 mg temozolomide.
- Temozolomide Hetero 180 mg is a size '0' capsule (opaque orange cap/white body) with '17' printed on the cap and 'H' on the body. Each capsule contains 180 mg temozolomide.
- Temozolomide Hetero 250 mg is a size '0 el' capsule (opaque white cap/white body) with '18' printed on the cap and 'H' on the body. Each capsule contains 250 mg temozolomide.

The hard capsules are packed in:
- Type I amber glass bottles with polypropylene child-resistant closures.
- Al-Al unit dose blisters, consisting of an OPA/Aluminium/PVC forming film and peelable Aluminium lidding foil with heat seal lacquer.

The excipients are:
Capsule content: anhydrous lactose, sodium starch glycolate type B, tartaric acid (E334), colloidal anhydrous silica and stearic acid (E570).
Capsule shell: gelatin, titanium dioxide (E171), sodium lauryl sulphate, indigo carmine (E132) (only the 5 mg and 140 mg strengths), iron oxide yellow (E172) (only the 5 mg and 20 mg strengths) and iron oxide red (E172) (only the 100 mg and 180 mg strengths).
Printing ink: shellac (E904), propylene glycol, potassium hydroxide and iron oxide black (E172)

The 20 mg, 100 mg, 140 mg, 180 mg and 250 mg strengths are fully dose proportional with regard to capsule filling. The 5 mg formulation differs from the other strengths. Hence relatively more filler (lactose) is used and relatively less active substance.

II.2 Drug Substance

The active substance is temozolomide, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.) but is described in the United States Pharmacopoeia (USP). Temozolomide is an off-white to light pink powder. It is sparingly soluble in dimethyl sulphoxide, slightly soluble in methanol and in water. Temozolomide is known to exist in several polymorphic forms. The polymorphic form of the active substance, used in the product at issue, is form III. It does not exhibit isomerism and is a non-hydroscopic compound.

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 five stages. The starting material was redefined and the ASMF updated accordingly. The process is described adequately and in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the USP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance has been provided for 7 batches stored at 2-8°C (up to 36 months) and 25°C/60% RH (6 months). After 36 months storage between 2-8°C, one out of specification was observed for related substances. The proposed retest period of 24 months at 2-8°C is justified in view of the results.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The primary goal 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 Temodal. To limit the risk for exposure (through dust particles by opening of the bottle and handling of the capsules) of persons in the environment to the cytotoxic material, dosing errors caused by pack size, and accidentally swallowing of the capsules by children, Al-Al unit dose blisters are used as additional packaging, which is acceptable. Pharmaceutical development has been adequately performed.

The MAH followed a biowaiver approach. *In vitro* comparative dissolution profiles were studied for all strengths of the reference and test product. For the 180 mg product additional *in vitro* studies demonstrated similarity for pH 6.8 as >85% was dissolved in 15 minutes.

Manufacturing process
A powder mass is dry mixed and subsequently 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 validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for batches of all capsule strengths in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, uniformity of dosage units, dissolution, water, assay, related substances, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from several batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two or three batches of each strength in accordance with applicable European guidelines testing the stability of the product for 6 months at 25°C/60% RH and up to 24 months at 40°C/75% RH. Tablets were stored in the proposed bottles. On basis of the data submitted, a shelf life was granted of 24 months. Results of in-use studies support an in-use shelf life of 7 days below 25°C. The photostability study performed as part of the stress studies did not result in any observed degradation.
For the product packed in Al-Al blister, a provisional shelf life of 12 months is accepted. This will be confirmed by results of stability studies.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate and gelatin used in the capsules are of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Temozolomide Hetero has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments was made:
- To carry out stability studies on Temozolomide capsules in the proposed Al-Al blister pack once batches have been produced.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Temozolomide Hetero is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Temodal which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

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 comprehensive justification based on the requirements described in the guideline on Investigation of Bioequivalence and scientific advice given by the MEB regarding the possibility of obtaining a biowaiver for this medicinal product.

IV.2 Pharmacodynamics

Biowaiver
A Biopharmaceutics Classification System (BCS) based biowaiver has been requested for all strengths. The BCS is a scientific framework to classify drugs on the basis of their aqueous solubility, permeability and dissolution. Drug substances can be classified in three classes according to the BCS:

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability

The BCS based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as an innovator product. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH was also required to show that the composition of the generic and innovator product is similar. In addition, a supportive discussion was provided about the therapeutic index of the product. Hence a BCS based biowaiver is applicable only for drugs which are not considered to have a narrow therapeutic index.

Solubility
Solubility of temozolomide was tested in different solvents/buffers (purified water, 0.1 N HCl, pH 4.5 acetate buffer and pH 7.5 phosphate buffer). Solubility is shown to be between 4.3 and 5.79 mg/ml. The results demonstrate that the highest 250 mg single dose is completely dissolved in 250 ml of buffers in the pH range 1.2 to 7.5.
It has been adequately demonstrated that the drug substance is highly soluble.

Permeability
Since the permeability of temozolomide was higher than the permeability of minoxidil, and minoxidil is at least 90% absorbed in humans, it can be inferred that temozolomide should have greater than 90% absorption in humans. Thus, temozolomide can be classified as highly permeable compound.

In vitro dissolution
Comparative dissolution testing for all strengths at three pH levels (0.1N HCl, pH 4.5 and pH 6.8) is provided and demonstrates >85% dissolution within 30 minutes for all strengths.

Qualitative and quantitative composition
The qualitative composition of the proposed product is identical to Temodal with the exception of the type of sodium starch glycolate (type A in Temodal vs type B in the proposed product). Both types can be considered similar with regard to functionality. The main difference is the pH of the dispersion of the product, which is slightly more acid for type B. However in view of the solubility of the active substance this is not regarded to have any influence.

Therapeutic index
Temozolomide is not considered a narrow therapeutic index drug.

Conclusion
Based on the available data temozolomide is considered to be BCS class 1 (high solubility and high permeability). The justification for BCS-based biowaiver is accepted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Temozolomide Hetero.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Opportunistic infections including Pneumocystis jirovecii pneumonia • Hypersensitivity reactions (including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and anaphylaxis) • Secondary malignancies • Genotoxicity • Hepatobiliary disorders
Important potential risks	• Drug exposure via semen • Pneumonitis • Cardiac disorders
Missing information	• Safety of temozolomide in patients with cardiac dysfunction • Safety of temozolomide in HIV positive patients • Safety of temozolomide in patients with severe hepatic impairment (Child's Class C) • Safety of temozolomide in patients with renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Temodal. No new clinical studies were conducted. No bioequivalence study was performed to support the application. Instead a BCS-based biowaiver was requested and granted. Dissolution is rapid and similar, and a difference in bioavailability is not expected. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the textual content, format, design lay out and wording of the PL of Levetiracetam Hetero, which has been approved on 17 January 2012 (PT/H/0515/001-004/DC) and is identical in textual content with the PL of Temodal. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Temozolomide Hetero hard capsules 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.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The BCS-based biowaiver is fully justified and accepted.

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 Hetero with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 2016.

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