COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Temozolomide Devatis 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules (temozolomide)

NL/H/5193/001-006/DC

Date: 15 November 2021

This module reflects the scientific discussion for the approval of Temozolomide Devatis 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules. The procedure was finalised at 8 July 2021. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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
EEA	European Economic Area
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 Devatis 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules, from Devatis GmbH.

The product is indicated for the treatment of:

- Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy 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 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules which have been registered in the EEA by Merck Sharp & Dohme Ltd since 26 January 1999 by the centralised procedure EMEA/H/C/000229.

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

- The 5 mg strength capsules are hard gelatin capsules with an opaque light green cap and an opaque white body imprinted with “5 mg”. Each hard capsule contains 5 mg temozolomide.
- The 20 mg strength capsules are hard gelatin capsules with a rich yellow cap and an opaque white body imprinted with “20 mg. Each hard capsule contains 20 mg temozolomide.
- The 100 mg strength capsules are hard gelatin capsules with a flesh-coloured cap and an opaque white body imprinted with “100 mg”. Each hard capsule contains 100 mg temozolomide.
- The 140 mg strength capsules are hard gelatin capsules with a transparent light blue cap and an opaque white body imprinted with “140 mg”. Each hard capsule contains 140 mg temozolomide.

- The 180 mg strength capsules are hard gelatin capsules with an opaque orange cap and an opaque white body imprinted with “180 mg”. Each hard capsule contains 180 mg temozolomide.
- The 250 mg strength capsules are hard gelatin capsules with an opaque white cap and an opaque white body imprinted with “250 mg”. Each hard capsule contains 250 mg temozolomide.

All capsule strengths are filled with white to light pink powder.

The hard capsules are packed in type III amber glass bottles with polypropylene child-resistant closures.

The excipients are:
Capsule content – lactose, sodium starch glycolate type A, stearic acid, tartaric acid and colloidal anhydrous silica.
Capsule shell – gelatin, titanium dioxide (E171), yellow iron oxide (E172) (only the 5 mg and 20 mg strengths), indigocarmine (E132) (only the 5 mg and 140 mg strengths) and red iron oxide (only the 100 mg and 180 mg strengths).
Printing ink – shellac, black iron oxide (E172), propylene glycol and ammonium hydroxide.

The 5 mg, 20 mg and 250 mg hard capsule strengths are qualitatively the same but not quantitatively proportional. The 100 mg, 140 mg, and 180 mg are fully dose proportional.

II.2 Drug Substance

The active substance is temozolomide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is sparingly soluble in water. Several polymorphic forms are reported for temozolomide. Consistent production of polymorph A and its stability through the shelf life has been adequately demonstrated.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

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 Ph.Eur. and the CEP, with additional requirements for residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions explained. The safety of each of the excipients and their quantities for use in the indicated paediatric population have been adequately addressed. The dissolution method indicated by the Food and Drug Administration for temozolomide has been selected. Due to the very rapid dissolution of the drug product, the discriminatory power of the method could not be shown. The MAH has applied for a BCS-based biowaiver, this is acceptable. The pharmaceutical development of the product has been adequately performed. The dosage form is found suitable for the paediatric population.

Manufacturing process

The main steps of the manufacturing process are pre-blending and wet granulation, blending and capsule filling. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches for each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. Functionality related characteristics have been discussed for lactose anhydrous, silica colloidal anhydrous and stearic acid. The specifications of the excipients 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 description, identification, uniformity of mass, disintegration, water content, uniformity of dosage unit, assay, dissolution, related substances and microbiological quality. The release and shelf-life specifications for all strengths are identical. A wider shelf-life limit for this impurity is acceptable. 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 on three full scaled batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

The currently identified sources of nitrosamine listed in the Q&A on "Information on nitrosamines for marketing authorisation holders" have been adequately addressed. No potential risk has been identified. No confirmatory testing is needed.

Stability of drug product

Stability data on the product have been provided on three batches for each strength stored at 25°C/60% RH (between 12 and 36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of 36 months. Photostability studies were not performed in accordance with ICH recommendations. However, no objection is made as the capsules should be kept in the original package to protect from moisture. There is no need for desiccant. The storage condition is 'Store below 25°C in the original bottle in order to protect from moisture. Keep the bottle tightly closed' is acceptable.

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

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 Devatis has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Temozolomide Devatis 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.

IV.2 Pharmacokinetics

BCS-based biowaiver

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), a BCS-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, i.e., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form."

A BCS-based biowaiver is requested by the MAH, claiming that temozolomide is a BCS class I drug. For such a biowaiver the following requirements should be met:

- The drug substance has been proven to exhibit high solubility and complete absorption (BCS class I). The solubility of temozolomide at the required pH of 1.2, 4.5 and 6.8 was between 6.1 and 6.2 mg/ml and demonstrated that the highest 250 mg single dose is completely dissolved in 250 ml of buffers in the pH range 1.2 to 6.8. High solubility has therefore been demonstrated. Posology states a dose of 200 mg/m^2 in adult and paediatric patients three years of age or older with recurrent or progressive malignant glioma. Assuming 200 mg/1.73 m^2, 400 mg dose may be relevant as well. Also for this dose, no issues related to solubility are expected. The pH was measured after solubilisation and was within reasonable distance from the initial pH. The requirement with respect to solubility is therefore met.

To demonstrate complete absorption of temozolomide in vivo further literature data from published studies is provided by the MAH. Based on the data from the six studies; US FDA summary, Newlands (1992), Marzolini (1998), Baker (1999), Brada (1999), and Dietz (2010) it

can be concluded that temozolomide is a highly absorbed drug and can be classified as a BCS-class1 drug.

- Excipients that might affect bioavailability are qualitatively and quantitatively the same.

Both the qualitative and quantitative composition of the generic and reference 5, 20, 100, 140, 180 and 250 mg capsules is considered sufficiently comparable. Further, excipients are not expected to directly affect the absorption of temozolomide.

- Either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated.

The complete dissolution data of 12 capsules required for the comparative dissolution testing between the test and reference product for each strength at pH 1.2, 4.5 and 6.8 being applied were provided. Dissolution similarity is confirmed as dissolution was more than 85% in 15 minutes at the 3 required pH in all the comparative testing.

- The drug should not have a narrow therapeutic index.

Temozolomide is not considered to be a narrow therapeutic index drug.

In conclusion, Temozolomide fulfils all conditions for a BCS-based biowaiver, which has therefore been granted

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 Devatis.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Myelosuppression - Opportunistic infections - Hypersensitivity reactions - Secondary malignancies including genotoxicity - Infusion site reactions - Hepatobiliary disorders and hepatic injury including fatal hepatic failure
Important potential risks	- Tissue damage - Interstitial - pneumonitis/pneumonitis - Reproductive and developmental toxicity - Drug exposure via semen - Cardiac Disorders
Missing information	- Use in HIV-positive patients - Use in patients with severe hepatic impairment - Use 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. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 Temodal, (EMEA/H/C/000229). 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 Devatis 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg, hard capsules. Temodal are well-known medicinal products with an established favourable efficacy and safety profile. Temozolomide is a BCS class 1 drug, and a BCS class biowaiver is granted.

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 Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 July 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse