Public Assessment Report

Decentralised Procedure

Temozolomide Zentiva 5 mg hard capsules
Temozolomide Zentiva 20 mg hard capsules
Temozolomide Zentiva 100 mg hard capsules
Temozolomide Zentiva 140 mg hard capsules
Temozolomide Zentiva 180 mg hard capsules
Temozolomide Zentiva 250 mg hard capsules

temozolomide

Procedure No: UK/H/5469/001-006/DC
(previously NL/H/2518/001-006/DC)

UK Licence No: PL 17780/0591-596

Winthrop Pharmaceuticals UK Limited
LAY SUMMARY

Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules. (temozolomide; hard capsules; 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg)

This is a summary of the Public Assessment Report (PAR) for Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules (PL 17780/0591-596; UK/H/5469/001-006/DC, previously NL/H/2518/001-006/DC). It explains how Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules.

For practical information about using Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules, patients should read the package leaflet or contact their doctor or pharmacist.

Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules may be referred to as Temozolomide Zentiva hard capsules in this report.

What are Temozolomide Zentiva hard capsules and what are they used for?
Temozolomide Zentiva hard capsules are medicines that contain the active substance temozolomide. Temozolomide Zentiva hard capsules are used for the treatment of patients with specific forms of brain tumours:
• Newly-diagnosed glioblastoma multiforme. Temozolomide is first used together with radiotherapy (concomitant phase of treatment) and after that, alone (monotherapy phase of treatment);
• Malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma. Temozolomide is used in these tumours if they return or get worse after standard treatment.

Temozolomide Zentiva hard capsules are ‘generic’ medicines. This means that Temozolomide Zentiva hard capsules are similar to reference medicines already authorised in the European Union (EU) called Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg Capsules (Schering Plough Europe, Belgium).

How are Temozolomide Zentiva hard capsules used?
Temozolomide are taken by mouth. For further information on how Temozolomide Zentiva hard capsules are used, please see the Summaries of Product Characteristics available on the MHRA website.

Temozolomide Zentiva hard capsules can only be obtained on prescription.

How do Temozolomide Zentiva hard capsules work?
Temozolomide is an antitumour agent.

How have Temozolomide Zentiva hard capsules been studied?
As Temozolomide Zentiva hard capsules are generic medicines, studies in patients have been limited to tests to determine that these capsules are bioequivalent to the reference medicines, Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg Capsules (Schering Plough Europe, Belgium). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Winthrop Pharmaceuticals UK Limited) has provided data from the published
literature on temozolomide.

What are the benefits and risks of Temozolomide Zentiva hard capsules?
Because Temozolomide Zentiva hard capsules are generic medicines and are bioequivalent to the reference medicines, their benefits and risks are taken as being the same as those of the reference medicines.

Why are Temozolomide Zentiva hard capsules approved?
It was concluded that, in accordance with EU requirements, Temozolomide Zentiva hard capsules have been shown to have comparable quality and to be bioequivalent to Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg Capsules (Schering Plough Europe, Belgium). Therefore, the view was that, as for Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250mg Capsules (Schering Plough Europe, Belgium), the benefits of these capsules outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Temozolomide Zentiva hard capsules?
Safety information has been included in the Summaries of Product Characteristics and the package leaflets for Temozolomide Zentiva hard capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Temozolomide Zentiva hard capsules.
Marketing Authorisations were granted in the UK on 22 February 2013.

The full PAR for Temozolomide Zentiva hard capsules follows this summary.

For more information about treatment with Temozolomide Zentiva hard capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in 12-2013.
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## Module 1
### Information about the initial procedure

| **Product Name(s)**                     | Temozolomide Zentiva 5 mg hard capsules  
|                                        | Temozolomide Zentiva 20 mg hard capsules  
|                                        | Temozolomide Zentiva 100 mg hard capsules  
|                                        | Temozolomide Zentiva 140 mg hard capsules  
|                                        | Temozolomide Zentiva 180 mg hard capsules  
|                                        | Temozolomide Zentiva 250 mg hard capsules |
| **Type of Application(s)**             | Generic, Article 10(1)  
| **Active Substance(s)**                | Temozolomide  
| **Form**                               | Capsule, hard  
| **Strength**                           | 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg  
| **MA Holder**                          | Winthrop Pharmaceuticals UK Limited  
|                                        | One Onslow Street, Guildford  
|                                        | Surrey, GU1 4YS  
|                                        | UK  
|                                        | Trading as:  
|                                        | Zentiva,  
|                                        | One Onslow Street,  
|                                        | Guildford, Surrey, GU1 4YS,  
|                                        | UK  
| **Reference Member State (RMS)**       | The Netherlands (NB: The role of RMS was transferred to the UK on 16 May 2013, after completion of the initial procedure).  
| **Concerned Member State (CMS)**       | UK (see above)  
| **Procedure Numbers**                  | NL/H/2518/001-006/DC (NB: The Procedure Numbers were changed to UK/H/5469/001-006/DC, with the change in RMS from the Netherlands to the UK).  
| **Timetable**                          | Day 211 – 18 January 2013 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Please note that representative labelling text for Temozolomide Zentiva 5 mg hard capsules (PL 17780/0591; UK/H/5469/001/DC) is shown below. The labelling text details for Temozolomide Zentiva 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules (PL 17780/0592-596; UK/H/5469/002-006/DC) are consistent with this text, with the exception of the Marketing Authorisation numbers and the strengths of the products. The MAH has committed to submitting mock-up livery to the relevant regulatory authorities for approval before marketing any other pack.
Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules

UK/H/5469/001-006/DC
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Netherlands and the UK considered that the applications for Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules (PL 17780/0591-596; NL/H/2518/001-006/DC [now UK/H/5469/001-006/DC]) could be approved. These are prescription-only medicines (POM) 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.

The applications were submitted using the Decentralised Procedure (DCP), with the Netherlands as Reference Member State (RMS), and the UK as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator medicinal products Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg Capsules (Schering Plough Europe, Belgium), which were authorised in the EEA via the Centralised Procedure (EU/1/98/096/001-012, EU/1/98/096/013-022 and EU/1/98/096/024-025) on 26 January 1999.

The active ingredient, temozolomide, an imidazotetrazine derivative, is a cytotoxic alkylating agent that undergoes spontaneous hydrolysis at physiological pH to its active metabolite 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC), which in turn degrades to a reactive methyl-diazonium cation and 5(4)-aminoimidazole-4(5)-carboxamide (AIC).

In January 2010, the Medicines Evaluation Board (MEB), the Netherlands, provided the applicant with scientific advice on the requirement of a bioequivalence study; the advice of conducting a study in glioma patients was followed. One bioequivalence study was submitted to support these applications, comparing the applicant’s test product Temozolomide 250 mg capsules with the reference product Temodal 250 mg capsules (Schering Plough Europe, Belgium) in glioma patients, under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No paediatric development programme was submitted or required for applications of this type.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The Netherlands and the UK considered that the applications could be approved at the end of the procedure (Day 211) on 18 January 2013. After a subsequent national phase, licences were granted in the UK on 22 February 2013. The role of RMS was transferred to the UK on 16 May 2013.

II. ABOUT THE PRODUCT

| Name(s) of the product in the Reference Member State | Temozolomide Zentiva 5 mg hard capsules  
Temozolomide Zentiva 20 mg hard capsules  
Temozolomide Zentiva 100 mg hard capsules  
Temozolomide Zentiva 140 mg hard capsules  
Temozolomide Zentiva 180 mg hard capsules  
Temozolomide Zentiva 250 mg hard capsules |
| Name(s) of the active substance(s) (INN) | Temozolomide |
| Pharmacotherapeutic classification (ATC code) | Antineoplastic agents - Other alkylating agents (ATC code: L01AX03) |
| Pharmaceutical form and strengths | Hard capsules; 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg |
| Reference number(s) for the Decentralised Procedure | NL/H/2518/001-006/DC (NB: The Procedure Numbers were changed to UK/H/5469/001-006/DC, with the transfer of the role of RMS from the Netherlands to the UK on 16 May 2013). |
| Reference Member State (RMS) | The Netherlands (NB: The role of RMS was transferred to the UK, after completion of the initial procedure). |
| Concerned Member State (CMS) | United Kingdom (see above) |
| Marketing Authorisation Number(s) | PL17780/0591-596 |
| Name and address of the authorisation holder | Winthrop Pharmaceuticals UK Limited  
One Onslow Street, Guildford  
Surrey, GU1 4YS  
UK  
Trading as:  
Zentiva,  
One Onslow Street,  
Guildford, Surrey, GU1 4YS,  
UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

ACTIVE SUBSTANCE

INN:    Temozolomide
Chemical Names:  3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5] tetrazine-8-carboxamide
Molecular formula:  C₆H₆N₆O₂
Structure:

\[
\begin{align*}
\text{CONH₂} \\
\text{N} & - \text{O} \\
\text{N} & - \text{N}
\end{align*}
\]

Mr:  194.06 g/mol
Appearance:  White to light tan/light pink non-hygroscopic powder.
Solubility:  Soluble in methanol and slightly soluble in water and acidic aqueous solutions (3.1 mg/ml).

Temozolomide is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients in the capsule, capsule shell and printing ink namely, lactose anhydrous, colloidal anhydrous silica, sodium starch glycollate (Type A), tartaric acid, stearic acid, gelatin, titanium dioxide (E 171), yellow iron oxide (E172; 5 mg, 20 mg and 180 mg strength capsules only), red iron oxide (E172; 20 mg, 100 mg and 180 mg strength capsules only), indigotine FD & C Blue 2 (E132; 5 mg, 100 mg and 140 mg strength capsules only), shellac, propylene glycol, purified water, sodium ammonia solution, potassium hydroxide and black iron oxide (E 172). Appropriate justification for the inclusion of each excipient has been provided.

With the exception of yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172), indigotine FD & C Blue 2 (E132), shellac, propylene glycol, purified water, sodium ammonia solution and potassium hydroxide], all excipients comply with their respective European Pharmacopoeia
monographs.

Yellow iron oxide (E172), red iron oxide (E172), shellac, sodium ammonia solution and potassium hydroxide are compliant with their respective United States-National Formulary monographs. Black iron oxide (E 172) is controlled to its United States-National Formulary monograph or to a suitable in-house specification. Indigotine FD & C Blue 2 (E132) is controlled to a suitable in-house specification. Propylene glycol and purified water are controlled to their respective United States Pharmacopoeia monographs. Certificates of Analysis have been provided for the pharmacopoeial excipients, showing compliance with the proposed specification.

With the exception of lactose anhydrous and gelatin, none of the excipients contain materials of animal or human origin.

The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious, stable hard capsules in the dosage strengths 5 mg, 20 mg, 100 mg, 140mg, 180 mg and 250 mg temozolomide, which were pharmaceutically equivalent to the originator products Temodal 5 mg, 20 mg, 100 mg, 140mg, 180 mg and 250 mg hard capsules (Schering-Plough Europe, Belgium). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution profiles have been provided for these products and the reference products Temodal 5 mg, 20 mg, 100mg, 140 mg, 180 mg and 250 mg hard capsules (Schering Plough Europe, Belgium).

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production-scale batches and has shown satisfactory results.

**Control of Finished Product**
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The capsules are packed in:
1. White opaque high-density polyethylene (HDPE) bottles with polypropylene (PE) push lock assembly closures, with polyester coil and dessicant, containing 5 capsules; or
2. Sachets composed of paper on linear low density polyethylene (LDPE, outermost layer), aluminium and ethylene acrylic acid co-polymer (innermost layer). Each sachet contains 1 hard capsule. The sachets are packaged in cardboard cartons containing 5 or 20 hard capsules.
Not all pack sizes may be market.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, the following shelf lives and storage conditions have been accepted:

1. A shelf life of 24 months for product packaged in HDPE bottles, with the storage conditions, ‘Store below 30°C. Store in the original bottle in order to protect from moisture. Keep the bottle tightly closed’;
2. A shelf life of 18 months for the 5 mg and 20 mg strength product packaged in sachets, with the storage conditions, ‘Store below 25°C’;
3. A shelf life of 18 months for the 100 mg, 140 mg, 180 mg and 250 mg strength product packaged in sachets, with the storage conditions, ‘Store below 30°C’.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**Bioequivalence/Bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

**Summaries of Product Characteristics (SmPCs), Product Information Leaflet (PIL) and Labels**

The SmPCs, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) Forms**

The MAA forms are satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

The grant of Marketing Authorisations is recommended.

**III.2 NON-CLINICAL ASPECTS**

As the pharmacodynamic, pharmacokinetic and toxicological properties of temozolomide are well-known, no new non-clinical data have been submitted and none are required.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). As the applications are for generic versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.

III.3  CLINICAL ASPECTS

Clinical Pharmacology

The clinical pharmacology of temozolomide is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted the following bioequivalence study to support the applications:

A randomised, open-label, two-sequence, two-treatment, two-period, single-dose crossover study comparing the test product Temozolomide 250 mg Capsules (EirGen Pharma Limited, Ireland) and the reference product Temodal (Schering Plough Europe, Belgium) in male and female patients with high grade glioma/astrocytoma, under fasting conditions.

Patients with high grade glioma/astrocytoma, eligible for administration of a 250 mg dose of temozolomide on days 1 and 2 of the first cycle of treatment were included. The patients were administered a single dose (250 mg of temozolomide) of either the test (A) or reference (B) product on Day 1 of treatment Cycle 1. This was followed by treatment with the other product (reference product if the test drug was given in first period and the test drug if reference product was given in the first period) on Day 2 of treatment Cycle 1. Drugs were administered with 240 ± 5ml of water, after an overnight fast of 10 hours. From days 3 to 5, an approved dose of 250 mg temozolomide was administered daily. From the second cycle onwards, the same dose of temozolomide was given at the dose of 175 mg/m² of body surface area for the first five days of every 4 weeks (28 days per cycle) until the patients completed all the six cycles oftherapy or disease progression, whichever was earlier.

The washout period between the treatment arms was 1 day.

During the pharmacokinetic determination days (days 1 and 2 of Cycle 1) blood sampling was performed pre-dose and up to 12 hours in each treatment period. The pharmacokinetic results are presented below:
Pharmacokinetic parameters (arithmetic mean ± SD, $t_{1/2}$, $t_{\text{max}}$ [median, range], ratios and confidence [CI] intervals) of temozolomide under fasted conditions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-t}$ microg/h/ml</th>
<th>$\text{AUC}_{0-\infty}$ microg/h/ml</th>
<th>$C_{\text{max}}$ microg/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$t_{1/2}$ h</th>
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<tr>
<td>Test</td>
<td>17.2 ± 7.0</td>
<td>18.4 ± 7.4</td>
<td>5.9 ± 2.5</td>
<td>1.25 (0.33-2.0)</td>
<td>1.7 ± 0.2</td>
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<tr>
<td>Reference</td>
<td>18.0 ± 7.8</td>
<td>19.1 ± 7.9</td>
<td>6.5 ± 3.0</td>
<td>1.0 (0.33-2.0)</td>
<td>1.7 ± 0.2</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>0.96 (0.91-1.02)</td>
<td>0.97 (0.91-1.02)</td>
<td>0.94 (0.86-1.01)</td>
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<tr>
<td>CV (%)</td>
<td>12.9</td>
<td>12.2</td>
<td>17.7</td>
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$\text{AUC}_{0-t}$: area under the plasma concentration-time curve from time zero to $t$ hours

$\text{AUC}_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity

$C_{\text{max}}$: maximum plasma concentration

$t_{\text{max}}$: time for maximum concentration

$t_{1/2}$: half-life

*ln-transformed values

Bioequivalence Conclusion
The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) defines the confidence limits as 80.00 to 125.00 % for AUC and $C_{\text{max}}$ values. Thus, the data support the claim that the applicant’s test product Temozolomide 250 mg Capsules is bioequivalent to the reference product Temodal 250 mg Capsules (Schering Plough Europe, Belgium) under fasting conditions.

As the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strengths of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), the results and conclusions of the bioequivalence study on the 250 mg strength can be extrapolated to the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strength hard capsules.

Efficacy
The efficacy of temozolomide is well-known. No new efficacy data have been submitted and none are required for these applications.

Safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for these applications. No new or unexpected safety issues arose during the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable from a clinical perspective. The SmPCs are consistent with those for the innovator products. The PIL is consistent with the details in the SmPCs and in line with current guidance. The labelling is in line with current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
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.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
The grant of Marketing Authorisations is recommended.

**IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Temozolomide Zentiva 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of temozolomide are well-known, no additional data were required.

No new non-clinical data were submitted and none are required for applications of this type.

**EFFICACY**
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 250 mg tablets and the reference product Temodal 250 mg Capsules (Schering Plough).

As the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strengths of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), the results and conclusions of the bioequivalence study on the 250 mg strength can be extrapolated to the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strength hard capsules.

**SAFETY**
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for these applications. As the safety profile of temozolomide is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

**PRODUCT LITERATURE**
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products, where appropriate and are in line with current guidance.

**BENEFIT/RISK ASSESSMENT**
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with temozolomide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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