Public Assessment Report

Decentralised Procedure

TEMOZOLOMIDE 5 MG HARD CAPSULES
TEMOZOLOMIDE RELIANCE 20 MG HARD CAPSULES
TEMOZOLOMIDE RELIANCE 100 MG HARD CAPSULES
TEMOZOLOMIDE RELIANCE 140 MG HARD CAPSULES
TEMOZOLOMIDE RELIANCE 180 MG HARD CAPSULES
TEMOZOLOMIDE RELIANCE 250 MG HARD CAPSULES
(temozolomide)

Procedure No: UK/H/5095/001-6/DC

UK Licence No: PL 42244/0001-0005, 0009

Reliance Genemedix Limited
This is a summary of the public assessment report (PAR) for Temozolomide 5 mg hard capsules (PL 42244/0009), Temozolomide Reliance 20 mg hard capsules (PL 42244/0001), Temozolomide Reliance 100 mg hard capsules (PL 42244/0002), Temozolomide Reliance 140 mg hard capsules (PL 42244/0003), Temozolomide Reliance 180 mg hard capsules (PL 42244/0004) and Temozolomide Reliance 250 mg hard capsules (PL 42244/0005). These medicinal products in most instances will be referred to as Temozolomide capsules in the remainder of this lay summary for ease of reading.

This summary explains how Temozolomide capsules were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Temozolomide capsules.

For practical information about using Temozolomide capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Temozolomide capsules and what are they used for?

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

Temozolomide 5 mg capsules are ‘hybrid medicines’. They are similar to a reference medicine containing the same active substance, but that differs in strength. The reference medicine for Temozolomide 5 mg capsules is Temodal 250 mg hard capsules.

Temozolomide Capsules are used to treat specific forms of brain tumours:
- In adults with newly-diagnosed glioblastoma multiforme. Temozolomide is first used together with radiotherapy (concomitant phase of treatment) and after that alone (monotherapy phase of treatment).
- In children 3 years and older and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma. Temozolomide is used in these tumours if they return or get worse after standard treatment.

How do Temozolomide capsules work?

Temozolomide capsules contain an active substance called temozolomide, which is an antitumour agent. Antitumour agents work by slowing down the growth of tumours.

How are Temozolomide capsules used?

Temozolomide capsules are hard capsules and the route of administration is oral.

These medicines can only be obtained with a prescription.
DCPAR Temozolomide hard capsules

The doctor will work out the exact dose of this medicine based on the size (height and weight) of the patient and if the patient has a recurrent tumour and has had chemotherapy treatment in the past. It is recommended to take the prescribed dose of temozolomide once a day, preferably at the same time each day. The capsule(s) should be taken on an empty stomach, for example, at least one hour before the patient plans to eat breakfast. The capsule(s) should be swallowed whole with a glass of water.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What the benefits of Temozolomide capsules have been shown in studies?

Temozolomide capsules can be considered bioequivalent to their respective reference medicines. Therefore, their benefits and risks are taken as being the same as the reference medicines.

What are the possible side effects of Temozolomide capsules?

Because Temozolomide capsules are either generic or hybrid medicines that have been shown to be considered similar to their respective reference medicines, Temodal 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg hard capsules, the benefits and possible side effects are taken as being the same as the reference medicines.

For a full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Temozolomide capsules, see Section 4 of the package leaflet available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are Temozolomide capsules approved?

The MHRA decided that the benefits of taking Temozolomide capsules outweigh the risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Temozolomide capsules?

A risk management plan has been developed to ensure that Temozolomide capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Temozolomide capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Temozolomide capsules

Germany and the UK agreed to grant Marketing Authorisations for Temozolomide Reliance 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules on 09 March 2014. Marketing Authorisations were granted in the UK on 17 April 2014 for Temozolomide Reliance 20 mg, 100 mg, 140 mg and 250 mg hard capsules and 25 April 2014 for Temozolomide Reliance 180 mg capsules.

Germany and the UK agreed to grant Marketing Authorisations for Temozolomide 5 mg capsules on 28 April 2017. A Marketing Authorisation was granted in the UK on 17 May 2017 in the UK.

The full PAR for Temozolomide capsules follows this summary. For more information about treatment with Temozolomide capsules, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Temozolomide Reliance 5mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules (PL 42244/0001-0005,0009; UK/H/5095/001-06/DC) could be approved. The applications were submitted via the Decentralised Procedures, with the UK as a Reference Member State (RMS) and Germany as a Concerned Member State (CMS).

These are prescription-only medicines (legal classification 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 for Temozolomide Reliance 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules were submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The application for Temozolomide 5 mg capsules was submitted according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application.

The reference products for the 20 mg, 100 mg, 140 mg, 180 mg and 250 mg strengths are Temodal 20 mg, 100 mg, 140 mg, 180 mg and 250 mg hard capsules (Schering-Plough; Europe), which were granted Marketing Authorisations in the EEA via the Centralised procedure (EU/1/98/096/003, EU/1/98/096/005, EU/1/98/096/009, EU/1/98/096/011, EU/1/98/096/007) on 26 January 1999. The reference product for the 5 mg strength is Temodal 250 mg hard capsules.

The active substance, temozolomide, is a triazine, which undergoes rapid chemical conversion at physiologic pH to the active, 5-(3-methyltriazene-1-yl) imidazole-4-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.

No new non-clinical studies were submitted for the generic applications Temozolomide Reliance 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules, or for the hybrid application Temozolomide 5mg capsules. This is acceptable as these applications concern medicinal products that will be used interchangeably with their respective reference products, which have been licensed for over 10 years. Further, the pharmacodynamic, pharmacokinetic and toxicological properties of temozolomide are well-known and temozolomide is a widely used active substance. A non-clinical overview based on a literature review is, thus, appropriate.

With the exception of the bioequivalence study comparing the pharmacokinetics of the test product Temozolomide 250 mg capsules versus the reference product Temodal 250 mg capsules (Schering-Plough Ltd, UK), no new clinical studies were conducted. This is acceptable as these applications concern medicinal products that will be used interchangeably with their respective reference products, which have been licensed for over 10 years. Further, the pharmacodynamic, pharmacokinetic and toxicological properties of temozolomide are well-known and temozolomide is a widely used active substance. A clinical overview based on a literature review is, thus, appropriate. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.
The RMS and CMS considered that the applications for Temozolomide Reliance 20 mg, 100 mg, 140 mg and 250 mg capsules could be approved at the end of procedure on 09 March 2014. After a subsequent national phase, Marketing Authorisations were granted in the UK on 17 April 2014 for Temozolomide Reliance 20 mg, 100 mg, 140 mg and 250 mg capsules and 25 April 2014 for Temozolomide Reliance 180 mg and capsules.

The RMS and CMS considered that the application for Temozolomide 5 mg capsules could be approved at the end of procedure on 28 April 2017. After a subsequent national phase, a Marketing Authorisation was granted in the UK on 17 May 2017.

**Summary of significant variations to the Marketing Authorisations:**
Temozolomide 20 mg, 100 mg, 140 mg, 180 mg and 250 mg capsules were authorised with a finished product shelf-life of 12 months. A variation to change the shelf life for these strengths from 12 months to 24 months was approved on 11 November 2014.
The 5 mg strength was authorised with a 24 month shelf life.
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II QUALITY ASPECTS

II.1 Introduction

Temozolomide 5mg hard capsules have an opaque white body, an opaque Green cap, and are imprinted with black ink. Each capsule contains 5 mg of the active ingredient temozolomide.

Temozolomide 20 mg hard capsules have an opaque white body, an opaque yellow cap, and are imprinted with black ink. Each capsule contains 20 mg of the active ingredient temozolomide.

Temozolomide 100 mg hard capsules have an opaque white body, an opaque pink cap, and are imprinted with black ink. Each capsule contains 100 mg of the active ingredient temozolomide.

Temozolomide 140 mg hard capsules have an opaque white body, a blue cap and are imprinted with black ink. Each capsule contains 140 mg of the active ingredient temozolomide.

Temozolomide 180 mg hard capsules have an opaque white body, an opaque brown cap, and are imprinted with black ink. Each capsule contains 180 mg of the active ingredient temozolomide.

Temozolomide 250 mg hard capsules have an opaque white body and cap and are imprinted with black ink. Each capsule contains 250 mg of the active ingredient temozolomide.

Other ingredients consist of the pharmaceutical excipients, as follows:

capsule content:
anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid

capsule shell:
Temozolomide 5 mg hard capsules: gelatin, titanium dioxide (E 171), patent blue V (E 131), sodium lauryl sulfate, yellow iron oxide (E 172),

Temozolomide 20 mg hard capsules: gelatin, titanium dioxide (E 171), sodium lauryl sulfate, yellow iron oxide (E 172),

Temozolomide 100 mg hard capsules: gelatin, titanium dioxide (E 171), sodium lauryl sulfate, red iron oxide (E 172),

Temozolomide 140 mg hard capsules: gelatin, titanium dioxide (E 171), sodium lauryl sulfate, carmosine (E 122), patent blue V (E 131)

Temozolomide 180 mg hard capsules: gelatin, titanium dioxide (E 171), sodium lauryl sulfate, yellow iron oxide (E 172), and red iron oxide (E 172),

Temozolomide 250 mg hard capsules: gelatin, titanium dioxide (E 171), sodium lauryl sulfate.

printing ink:
shellac, propylene glycol, strong ammonia solution, potassium hydroxide, purified water and black iron oxide (E 172).
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With the exception of the printing ink, all excipients used comply with their respective European Pharmacopoeia monographs. The printing ink is controlled to an in-house specification.

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

The supplier of lactose anhydrous has confirmed that the milk used in the production of lactose anhydrous 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 anhydrous.

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 products.

The finished products are packaged in Type III amber glass bottles with polypropylene child-resistant closures. Each bottle contains 5 hard capsules.

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

II.2 Drug Substance

Temozolomide

INN: Temozolomide

Chemical name: 3, 4-Dihydro-3-methyl-4-oxoimidazo [5, 1- d][1,2,3,5-tetrazine-8- carboxamide or 3-methyl-8-aminocarbonylimidazo [5, I-d]-I, 2, 3, 5-tetrazin- 4 (3H)-one

Structure:

![Structure](image)

Molecular formula: C\text{6}H\text{6}N\text{6}O\text{2}

Molecular weight: 194.15 g/mol

Appearance: White to light pink powder

Solubility: Soluble in dimethyl sulfoxide, sparingly soluble in water, practically insoluble in toluene

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
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Specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance temozolomide, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory specifications have been provided for all packaging used for storing active temozolomide. The primary packaging has been shown to comply with current legislation concerning contact with food.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. A suitable retest period has been set based on stability data submitted for the active substance stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate acceptable, stable and bioequivalent products that could be used interchangeably instead of the reference products Temodal 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 200 mg hard capsules (Schering-Plough; Europe). A satisfactory account of the pharmaceutical development has been provided for these applications.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on three commercial-scale batches of each strength of finished product. The results are satisfactory.

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

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. At the time of grant, the results from these studies supported a shelf-life for the 20 mg, 100 mg, 140 mg, 180 mg and 200 mg strengths of 12 months, with the storage conditions "Do not store above 30 °C", "store in the original bottle in order to protect from moisture" and "keep the bottle tightly closed". A variation to change the shelf life for these strengths from 12 months to 24 months was approved on 11 November 2014.
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More long-term stability data was provided with the application for the 5 mg strength, supporting a shelf-life of 24 months with the storage conditions “Do not store above 30 °C”, “store in the original bottle in order to protect from moisture” and “keep the bottle tightly closed”.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these products from a pharmaceutical perspective.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of temozolomide are well-known. No new non-clinical data have been submitted for these applications

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
The pharmacology of temozolomide is well-known and adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of temozolomide are well-known and adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of temozolomide are well-known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/environmental risk assessment (ERA)
As these products are intended for generic substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these products from a non-clinical perspective.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of temozolomide is well-known. With the exception of data from the bioequivalence study detailed below, no new clinical data are provided or are required for these applications.

IV.2 Pharmacokinetics
With the exception of the below study, no new pharmacokinetic or pharmacodynamic data have been submitted with these applications and none are required.

In support of these applications, the applicant has submitted the following bioequivalence study:

A multicentre, randomised open-label, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study to compare the pharmacokinetics of the test product Temozolomide 250 mg
DCPAR Temozolomide hard capsules capsule (Reliance Life Sciences, India) versus the reference product Temodal 250 mg capsule of (Schering-Plough Ltd, UK) in adult male and/or female cancer patients under fasting conditions.

The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.

Patients with glioma/astrocytoma, eligible for administrations or already receiving a 250 mg dose of temozolomide were included. The patients were administered a single dose (250 mg of temozolomide) of either the test or reference product after fasting conditions of at least 10 hours, with 240 ml of water. A washout period of 24 hours was maintained between dosing. Blood samples were taken pre-dose and up to 10 hours post dose.

A summary of the main pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>24</td>
<td>7.37</td>
<td>2.54</td>
<td>2.35</td>
<td>6.9</td>
<td>14.9</td>
<td>34.51</td>
</tr>
<tr>
<td>$\text{AUC}_{0-19}$</td>
<td>24</td>
<td>21.09</td>
<td>3.9</td>
<td>14.25</td>
<td>20.88</td>
<td>31.31</td>
<td>18.47</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>24</td>
<td>22.04</td>
<td>3.93</td>
<td>14.95</td>
<td>21.81</td>
<td>32.78</td>
<td>17.82</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>24</td>
<td>1.3</td>
<td>0.91</td>
<td>0.33</td>
<td>1.25</td>
<td>4</td>
<td>69.86</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>24</td>
<td>1.83</td>
<td>0.24</td>
<td>1.26</td>
<td>1.77</td>
<td>2.27</td>
<td>13.18</td>
</tr>
<tr>
<td>$K_{el}$</td>
<td>24</td>
<td>0.39</td>
<td>0.05</td>
<td>0.31</td>
<td>0.39</td>
<td>0.55</td>
<td>14.06</td>
</tr>
</tbody>
</table>

The 90% confidence interval of the test/reference ratio for the $\text{AUC}_{0-19}$ and $C_{\text{max}}$ was within the pre-defined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion, bioequivalence has been demonstrated between the test and reference products. Thus, the data supports the claim that the applicant’s test product Temozolomide 250 mg capsules is bioequivalent to the reference product Temodal 250 mg capsules, under fasting conditions.

### Biowaiver

The applicant applied for Biopharmaceutics Classification System (BCS) based biowaiver. This was considered acceptable because confirmation was given that Temozolomide 5 mg, 20 mg, 100 mg, 140 mg and 180 mg capsules meet all the conditions which are stated in Biopharmaceutics Classification System (BCS) biowaiver guideline. The results of the pharmacokinetics study are, therefore, considered applicable to the 5 mg, 20 mg, 100 mg, 140 mg and 180 mg strengths.

### Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for these types of applications.
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IV.5 Clinical efficacy
No new data on efficacy have been submitted and none are required for these types of applications.

IV.6 Clinical safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues arose during the bioequivalence study.

IV.7 Risk Management Plan (RMP)
The applicant has submitted a Risk Management Plan (RMP), 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 this product.

A summary of safety concerns, as approved in the RMP is provided below:

<table>
<thead>
<tr>
<th>Important identified risks (s)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myelosuppression</td>
<td></td>
</tr>
<tr>
<td>• Opportunistic infections</td>
<td></td>
</tr>
<tr>
<td>• Hypersensitivity reactions (including erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and anaphylaxis)</td>
<td></td>
</tr>
<tr>
<td>• Secondary malignancies</td>
<td></td>
</tr>
<tr>
<td>• Genotoxicity</td>
<td></td>
</tr>
<tr>
<td>• Hepatobiliary disorders</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• None</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients positive for HIV infection</td>
<td></td>
</tr>
<tr>
<td>• Paediatric population (1)</td>
<td></td>
</tr>
<tr>
<td>• Patients with severe hepatic impairment (1)</td>
<td></td>
</tr>
<tr>
<td>• Patients with renal impairment (1)</td>
<td></td>
</tr>
<tr>
<td>• Pregnant and lactating mothers (1)</td>
<td></td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of these products from a clinical perspective.

V User consultation
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.
A bridging report has been submitted by the applicant for the subsequent application of the 5 mg strength, making reference to the user testing submitted for the Temozolomide 20 mg, 100 mg, 140 mg, 180 mg and 250 mg Reliance capsules, UK/H/5095/001-005/DC, which is acceptable.

IV Overall conclusion, benefit/risk assessment and recommendation
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 products are bioequivalent to the marketed reference products and their benefits and risks are considered similar. The benefit/risk balance is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Package Leaflet and Labels
In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPCs) and package leaflets for the products granted Marketing Authorisations at a national level are available on the MHRA website.

The currently approved labelling for all strengths of Temozolomide capsules is presented below:
DCPAR Temozolomide hard capsules

Each hard gelatin capsule contains:
Temozolomide........................................100 mg
Also contains anhydrous lactose. See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store in the original package. Do not store above 30°C. Protect from moisture.
Keep out of the sight and reach of children.
Oral use. Read the package leaflet before use.
Store in the original package. Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
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Store in the original package. Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
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DCPAR Temazolomide hard capsules

Each hard gelatin capsule contains:
Temazolomide.................. 100 mg

Also contains amyllose lactose,
See package leaflet for further information.
Oral use. Read the package leaflet before use.
Store in the original package. Do not store above 30°C.
Keep the bottle tightly closed in order to protect from
moisture.
Keep out of the sight and reach of children,
preferably in a locked cupboard.
Accidental ingestion can be lethal for children.

Cytosis: Do not open, crush or chew
the capsule, swallow whole. If a capsule is damaged,
avoid contact with your skin, eyes or nose.

Reliance
GeneMedix

Marketing Authorization Holder:
Reliance GeneMedix Limited
8th floor, 165 Wigmore Street
London W1U 1QY, UK

PL 42244/0002
Lot : 
Exp. Date :
Table of content of the PAR update
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update shelf life of the finished product from 12 months to 24 months. Consequently section 6.3 (Shelf life) of the SmPC has been updated.</td>
<td>UK/H/5095/001-005/IB/0002</td>
<td>SmPC</td>
<td>10/11/2014</td>
<td>11/11/2014</td>
<td>Approved</td>
<td>N</td>
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</tbody>
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