Public Assessment Report

Decentralised Procedure

SYNCLORAL 10, 25, 50 AND 100 MG CAPSULES, SOFT
EMULSOFORAL 10, 25, 50 AND 100 MG CAPSULES, SOFT
(ciclosporin)

Procedure No:
UK/H/5195/001-004/DC
UK/H/5196/001-004/DC

UK Licence No:
PL 00289/1732-35
PL 00289/1736-39

Teva UK Limited
LAY SUMMARY

On 23 May 2013, Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway, Romania (25, 50 and 100 mg strengths only), Sweden, and the UK agreed to grant Marketing Authorisations to Teva UK Limited for the medicinal products Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1732-35; UK/H/5195/001-4/DC).

In a parallel procedure the Netherlands and the UK also agreed to grant Marketing Authorisations for Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1736-39; UK/H/5196/001-4/DC).

The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 28 June 2013.

These are prescription-only medicines (legal status POM) containing the active ingredient ciclosporin. Ciclosporin is an immunosuppressant and is used to prevent rejection of newly transplanted organs such as liver, kidney, heart, lung and pancreas, or bone marrow transplants. It is also used for the treatment of severe psoriasis, kidney disease due to some forms of nephrotic syndrome, severe rheumatoid arthritis and severe eczema (atopic dermatitis). Ciclosporin works by suppressing the immune system and reducing inflammation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ciclosporin 10, 25, 50 and 100 mg Capsules, soft, outweigh the risks and Marketing Authorisations were granted.

On 15 January 2014, a variation was approved to change the name of the products Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1732-35; UK/H/5195/001-4/DC) to Syncloral 10, 25, 50 and 100 mg Capsules, soft, in the UK only.

On 16 January 2014, a variation was approved to change the name of Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1736-39; UK/H/5196/001-4/DC) to Emulsoforal 10, 25, 50 and 100 mg Capsules, soft, in the UK only.

The product names Ciclosporin 10, 25, 50 and 100 mg Capsules, soft, will be used throughout this Public Assessment Report as this report is based on the original assessment of these applications, which were granted with the name Ciclosporin.
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<td>25</td>
</tr>
</tbody>
</table>
# Module 1

**Information about initial procedure**

| **Product Name** | Ciclosporin 10, 25, 50 and 100 mg Capsules, soft
| **Type of Application** | Generic, Article 10(1)
| **Active Substances** | Ciclosporin
| **Form** | Soft capsules
| **Strength** | 10 mg, 25 mg, 50 mg and 100 mg
| **MA Holder** | Teva UK Limited
| | Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK
| **Reference Member State (RMS)** | UK

**Concerned Member States (CMS)**

- UK/H/5195/001/DC: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway and Sweden
- UK/H/5195/002-4/DC: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway, Sweden and Romania
- UK/H/5196/001-4/DC: The Netherlands

| **Procedure Number** | UK/H/5195-6/001-4/DC
| **Timetable** | Day 210 – 23 May 2013
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been 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 for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the currently approved label text. No label mock-ups have been provided for these products. In accordance with medicines legislation, these products shall not be marketed in the UK until approval of the label mock-ups has been obtained.

Please see below an example of label text for the product licence PL 00289/1732. The label texts for PL 00289/1733-35 are consistent with this:

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT

Syncloral 10 mg Capsules, soft

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Outer carton

---

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncloral 10 mg Capsules, soft</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each soft capsule contains 10 mg ciclosporin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains ethanol and sorbitol (E420). Please see the enclosed leaflet for further information.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule, soft</td>
</tr>
<tr>
<td>20 soft capsules</td>
</tr>
<tr>
<td>50 soft capsules</td>
</tr>
<tr>
<td>50 soft capsules</td>
</tr>
<tr>
<td>50x1 soft capsules</td>
</tr>
<tr>
<td>60 soft capsules</td>
</tr>
<tr>
<td>60x1 soft capsules</td>
</tr>
<tr>
<td>90 soft capsules</td>
</tr>
<tr>
<td>100 soft capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Swallow the capsules whole.</td>
</tr>
<tr>
<td>Please read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>8. EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Do not freeze. Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1732

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Syncloral 10 mg Capsules, soft
Please see below an example of label text for the product licence PL 00289/1736. The label texts for PL 00289/1737-39 are consistent with this:

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blister</strong></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Emulsoforal 10 mg Capsules, soft

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Teva UK Ltd

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Lot

5. **OTHER**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Emulsoforal 10 mg Capsules, soft

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 10 mg ciclosporin.

3. LIST OF EXCIPIENTS

Contains ethanol and sorbitol (E420). Please see the enclosed leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, soft

20 soft capsules
30 soft capsules
50 soft capsules
60 soft capsules
90 soft capsules
100 soft capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the capsules whole.
Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Store below 30°C. Do not freeze. Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1736

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Emulsoforal 10 mg Capsules, soft
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1732-39; UK/H/5195-6/001-4/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and the following Concerned Member States (CMS):

PL 00289/1732; UK/H/5195/001/DC: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway and Sweden

PL 00289/1733-35; UK/H/5195/002-4/DC: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway, Sweden and Romania

PL 00289/1736-39; UK/H/5196/001-4/DC: The Netherlands

These products are prescription-only medicines (legal classification POM).

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Neoral 10, 25, 50 and 100 mg Soft Gelatin Capsules (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals), which were initially granted Marketing Authorisations in the UK on 27 March 1995 (25 mg, 50 mg and 100 mg strengths) and 03 April 1998 (10 mg strength). The reference product used in the bioequivalence studies was Sandimmun Optoral 100 mg Weichkapseln (Novartis Pharma GmbH, Germany).

Ciclosporin is indicated for the prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas transplants; for the treatment of transplant rejection in patients previously receiving other immunosuppressive agents; for the prevention of graft rejection following bone marrow transplantation and for the prophylaxis or treatment of graft-versus-host disease (GVHD). Ciclosporin can also be used for the treatment of nephrotic syndrome; for severe, active rheumatoid arthritis, where classical, disease modifying anti-rheumatic drugs are inappropriate or ineffective; and for severe forms of psoriasis and severe atopic dermatitis where conventional therapy is inappropriate or ineffective.

These products contain the active ingredient ciclosporin. Ciclosporin is a cyclic polypeptide, consisting of 11 amino acids. It is a strong immunosuppressive substance, which acts specifically and reversibly on lymphocytes. It blocks resting lymphocytes in the G0 or G1 phase of the cell cycle and inhibits the antigen triggered release of lymphokines from activated T-cells. Unlike cytostatic agents, ciclosporin does not suppress haemopoiesis and has no effect on phagocytic cell function.

No non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Two bioequivalence studies were performed, which compared the pharmacokinetics of Ciclosporin 100 mg Capsules, soft (the test product) with Sandimmun Optoral 100 mg Weichkapseln (the reference
product) under both fed and fasting conditions. The bioequivalence studies were 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 this product.

The RMS and CMS considered that the applications could be approved with the end of procedure on 23 May 2013. After a subsequent national phase, licences were granted in the UK on 28 June 2013.

On 15 January 2014, a variation was approved to change the name of the products Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1732-35; UK/H/5195/001-4/DC) to Syncloral 10, 25, 50 and 100 mg Capsules, soft, in the UK only.

On 16 January 2014, a variation was approved to change the name of the products Ciclosporin 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1736-39; UK/H/5196/001-4/DC) to Emulsoforal 10, 25, 50 and 100 mg Capsules, soft, in the UK only.

The product names Ciclosporin 10, 25, 50 and 100 mg Capsules, soft, are used throughout this Public Assessment Report, as this report is based on the original assessment of these applications, which were granted with the name Ciclosporin.
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ciclosporin 10, 25, 50 and 100 mg Capsules, soft Ciclosporin 10, 25, 50 and 100 mg Capsules, soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification</td>
<td>Immunosuppressive agents, calcineurin inhibitors (L04AD01)</td>
</tr>
<tr>
<td>(ATC code)</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Soft capsules 10 mg, 25 mg, 50 mg and 100 mg</td>
</tr>
</tbody>
</table>
| Reference numbers for the Decentralised Procedure | UK/H/5195/001-4/DC  
UK/H/5196/001-4/DC |
| Reference Member State                        | UK                                                                                               |
| Member States concerned                      | UK/H/5195/001/DC:  
Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway and Sweden  
UK/H/5195/002-4/DC: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Ireland, Iceland, Lithuania, Luxembourg, Latvia, Malta, Norway, Sweden and Romania  
UK/H/5196/001-4/DC:  
The Netherlands  
UK/H/5196/002-4/DC:  
The Netherlands |
| Marketing Authorisation Number(s)             | PL 00289/1732-35  
PL 00289/1736-39 |
| Name and address of the authorisation holder  | Teva UK Limited  
Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Ciclosporin

rINN: Ciclosporin


Structure:

![Chemical structure of Ciclosporin](image)

Molecular formula: C_{62}H_{111}N_{11}O_{12}

Molecular weight: 1202.6

Appearance: White or almost white odourless powder, which is insoluble in water and n-hexane, and soluble in methanol, ethanol, acetone and chloroform

All aspects of the manufacture and control of ciclosporin are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely macrogolglycerol hydroxystearate, glycerol monolinoleate, diethylene glycol monoethyl ether, anhydrous ethanol, D,L-α-tocopherol, gelatin, glycerol (85%), sorbitol liquid (non-crystallising; E420), glycine, titanium dioxide (E171), light liquid paraffin, printing ink (consisting of shellac (E904), propyl glycol, concentrated ammonia solution, indigo carmine (E132)). Brown iron oxide is an additional excipient for the 100 mg strength product and yellow iron oxide for the 25 mg and 50 mg strengths.

With the exception of the printing ink, and the yellow and brown iron oxide, which comply with suitable in-house standards, all excipients comply with their respective European Pharmacopoeia monographs.

With the exception of gelatin, none of the excipients are sourced from animal or human origin. Suitable EDQM certificates of suitability have been provided for all suppliers of gelatin to show that this is produced in line with current European guidelines concerning the minimisation of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of these products.
Pharmaceutical Development
The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the currently licensed products, Neoral 10, 25, 50 and 100 mg Soft Gelatin Capsules (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed products and their respective 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 production-scale batches of each of the four strengths 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.

Container-Closure System
The finished product is packaged in oriented polyamide/aluminium/polyvinylchloride blisters in pack sizes of 20, 30, 50, 50x1, 60, 60x1, 90 and 100 soft capsules. The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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 food.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on commercial-scale batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with the storage conditions, “Store below 30°C. Do not freeze.” and “Store in the original pack to protect from moisture and light”.

Bioequivalence/bioavailability
Bioequivalence studies were carried out to compare the pharmacokinetics of Ciclosporin 100 mg Capsules, soft (the test product) with Sandimmun Optoral 100 mg Weichkapseln (the reference product) under both fed and fasting conditions.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC and text versions of the PIL and labels are acceptable from a pharmaceutical perspective.

The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Ciclosporin 10 mg, 25 mg, 50 mg and 100 mg Capsules, soft was provided. 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) form**
The MAA forms are satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

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

### III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ciclosporin are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### Pharmacokinetics

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence studies:

**Study 1- Fasting Conditions**

An open-label, single-dose, randomised, two-period, two-sequence, two-treatment, crossover study, to compare the bioavailability of the test product, Ciclosporin 100 mg Soft Gelatin Capsules (Teva Czech Industries) with the reference product, Sandimmun Optoral 100 mg Weichkapseln (Novartis Pharma GmbH, Germany), in healthy male and female subjects under fasting conditions.

Volunteers were given each treatment after an overnight fast. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post-dose. Each regimen was separated by a 7-day washout period.
The pharmacokinetic results for plasma levels of ciclosporin under fasting conditions are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trt</th>
<th>n</th>
<th>Arithmetic Mean (CV %)</th>
<th>Geometric Mean</th>
<th>Contrast Ratio (%)</th>
<th>90% Confidence Interval</th>
<th>Intra-Subj CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>A</td>
<td>62</td>
<td>655.02 (22)</td>
<td>638.81</td>
<td>A vs B</td>
<td>103.82</td>
<td>99.63 - 108.18</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>62</td>
<td>635.81 (25)</td>
<td>615.32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AUCt</td>
<td>A</td>
<td>62</td>
<td>1900.93 (25)</td>
<td>1845.74</td>
<td>A vs B</td>
<td>101.67</td>
<td>99.26 - 104.14</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>62</td>
<td>1871.41 (25)</td>
<td>1815.43</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tmax</td>
<td>A</td>
<td>62</td>
<td>1.53 (30)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>62</td>
<td>1.47 (27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The pharmacokinetic results for plasma levels of ciclosporin under fed conditions are presented below:

Compared with the reference product, the 90 % confidence intervals for the test product (A versus B) are within 90.00-111.11 % for Cmax and AUC. The test and reference product can therefore be considered to be bioequivalent under fasting conditions.

**Study 2- Fed Conditions**

An open-label, single-dose, randomised, four-period, two-sequence, two-treatment, replicate crossover study, to compare the bioavailability of the test product, Ciclosporin 100 mg Soft Gelatin Capsules (Teva Czech Industries) with the reference product, Sandimmun Optoral 100 mg Weichkapseln (Novartis Pharma GmbH, Germany), in healthy male and female subjects under fed conditions.

After a fast of at least 10 hours, volunteers were given a high fat, high calorie breakfast. Treatments were given 30 minutes after the breakfast. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 24 hours post-dose. Each regimen was separated by a 7-day washout period.

The pharmacokinetic results for plasma levels of ciclosporin under fed conditions are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRT</th>
<th>Means</th>
<th>Contrast</th>
<th>Ratio</th>
<th>90% CI</th>
<th>Intra-Subj CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arithmetic</td>
<td>CV %</td>
<td>Geometric</td>
<td>A vs B</td>
<td>Lower</td>
</tr>
<tr>
<td>AUCt</td>
<td>A₁</td>
<td>1525.5</td>
<td>31</td>
<td>1472.7</td>
<td>A vs B</td>
<td>102.30</td>
</tr>
<tr>
<td></td>
<td>A₂</td>
<td>1565.0</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>B₁</td>
<td>1491.0</td>
<td>30</td>
<td>1439.6</td>
<td>A vs B</td>
<td>102.30</td>
</tr>
<tr>
<td></td>
<td>B₂</td>
<td>1501.9</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cmax</td>
<td>A₁</td>
<td>413.3</td>
<td>51</td>
<td>372.9</td>
<td>A vs B</td>
<td>102.31</td>
</tr>
<tr>
<td></td>
<td>A₂</td>
<td>436.8</td>
<td>51</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>B₁</td>
<td>413.0</td>
<td>50</td>
<td>364.5</td>
<td>A vs B</td>
<td>102.31</td>
</tr>
<tr>
<td></td>
<td>B₂</td>
<td>402.4</td>
<td>48</td>
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</table>

Compared with the reference product, the 90 % confidence intervals for the test product (A versus B) are within 90.00-111.11 % for Cmax and AUC. The test and reference product can therefore be considered to be bioequivalent under fed conditions.
Overall bioequivalence study conclusion
Ciclosporin 100 mg Capsules can be considered bioequivalent with Sandimmun Optoral 100 mg Weichkapseln.

As the 10 mg, 25 mg 50 mg and 100 strengths of the product meet the bio-waiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 100 mg strength can be extrapolated to the 10 mg, 25 mg and 50 mg capsules.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

Safety
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

SmPC, PIL and Labels
The SmPC and text versions of the PIL and labels are acceptable from a clinical perspective and consistent with those for the reference products, where appropriate.

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.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of Marketing Authorisations is recommended.
IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ciclosporin 10, 25, 50 and 100 mg Capsules, soft 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 and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product Sandimmun Optoral 100 mg Weichkapseln (Novartis Pharma GmbH, Germany).

As the 10 mg, 25 mg 50 mg and 100 strengths of the product meet the bio-waiver criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 100 mg strength can be extrapolated to the 10 mg, 25 mg and 50 mg capsules.

No new or unexpected safety concerns arose from these applications.

The SmPC and text versions of the PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with ciclosporin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists some non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>11/11/2013</td>
<td>Type IB</td>
<td>For PL 00289/1732-35 only: To change the name of the finished medicinal products to Syncloral 10 mg, 25 mg, 50 mg and 100 mg Capsules, soft, in the UK only. As a consequence, section 1 and 4.2 of the UK SmPC, label and PIL have been updated.</td>
<td>Granted 15/01/2014</td>
</tr>
<tr>
<td>11/11/2013</td>
<td>Type IB</td>
<td>For PL 00289/1736-39 only: To change the name of the finished medicinal products to Emulsoforal 10 mg, 25 mg, 50 mg and 100 mg Capsules, soft, in the UK only. As a consequence, section 1 and 4.2 of the UK SmPC, label and PIL have been updated.</td>
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<td>06/01/2014</td>
<td>Type IB</td>
<td>To update sections 2 (Qualitative and quantitative composition), 4 (Clinical particulars) and 5 (Pharmacological properties) of the SmPC and leaflet in line with Article 30 procedure (EMEA/H/A-30/1300, EMEA/H/A-30/1320)</td>
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Annex 1

Reference:  
PL 00289/1732 - 0003  
PL 00289/1733 - 0003  
PL 00289/1734 - 0003  
PL 00289/1735 - 0003

Product:  
Ciclosporin 10 mg Capsules, soft  
Ciclosporin 25 mg Capsules, soft  
Ciclosporin 50 mg Capsules, soft  
Ciclosporin 100 mg Capsules, soft

Marketing Authorisation Holder:  
Teva UK Limited

Active Ingredient:  
Ciclosporin

Reason  
To change the name of the finished medicinal product to Syncloral 10 mg, 25 mg, 50 mg and 100 mg Capsules, soft, in the UK only. As a consequence, section 1 and 4.2 of the UK SmPC, label and PIL have been updated.

Supporting evidence  
The applicant has submitted a revised SmPC, label text and PIL text for the UK only.

Evaluation  
The choice of a UK invented name of Syncloral is considered acceptable for these products. The amendments to the SmPC, PIL text and label text are acceptable.

Conclusion  
The amendments to the product names, SmPC fragments, leaflet text and label text can be approved.

Currently, this product is not marketed in the UK. The MAH has committed to the submission and approval of PIL and label mock-ups prior to marketing.

Decision: Approved (15/01/2014).
Annex 2

Reference:
- PL 00289/1736 - 0003
- PL 00289/1737 - 0003
- PL 00289/1738 - 0003
- PL 00289/1739 - 0003

Product:
- Ciclosporin 10 mg Capsules, soft
- Ciclosporin 25 mg Capsules, soft
- Ciclosporin 50 mg Capsules, soft
- Ciclosporin 100 mg Capsules, soft

Marketing Authorisation Holder: Teva UK Limited
Active Ingredient: Ciclosporin

Reason
To change the name of the finished medicinal products to Emulsoforal 10 mg, 25 mg, 50 mg and 100 mg Capsules, soft, in the UK only. As a consequence, section 1 and 4.2 of the UK SmPC, label and PIL have been updated.

Supporting evidence
The applicant has submitted a revised SmPC, label text and PIL text for the UK only.

Evaluation
The choice of a UK invented name of Emulsoforal is considered acceptable for these products. The amendments to the SmPC, PIL text and label text are acceptable.

Conclusion
The amendments to the product names, SmPC fragments, leaflet text and label text can be approved.

Currently, this product is not marketed in the UK. The MAH has committed to the submission and approval of PIL and label mock-ups prior to marketing.

Decision: Approved (16/01/2014).
Annex 3

Reference:
- PL 00289/1732 - 0005
- PL 00289/1733 - 0005
- PL 00289/1734 - 0005
- PL 00289/1735 - 0005
- PL 00289/1736 - 0004
- PL 00289/1737 - 0004
- PL 00289/1738 - 0004
- PL 00289/1739 - 0004

Product:
- Syncoral 10, 25, 50 and 100 mg Capsules, soft
- Emulsoforal 10, 25, 50 and 100 mg Capsules, soft

Marketing Authorisation Holder:
Teva UK Limited

Active Ingredient:
Ciclosporin

Reason
To update sections 2 (Qualitative and quantitative composition), 4 (Clinical particulars) and 5 (Pharmacological properties) of the SmPCs and leaflets in line with Article 30 procedure (EMEA/H/A-30/1300, EMEA/H/A-30/1320).

Supporting evidence
The applicant has submitted revised sections of the SmPCs and PILs.

Evaluation
The updated SmPCs and PILs are satisfactory.

Conclusion
The variations were approved on 7th April 2014 (PL 00289/1732-1735) and 8th April 2014 (PL 00289/1736-1739) and updated SmPCs fragments and the PILs have been incorporated into these Marketing Authorisations.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs) Updated

Following approval of the variations on 7th April 2014 (PL 00289/1732-1735) and on 8th April 2014 (PL 00289/1736-1739) the SmPCs were updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET (PIL) Updated

Following approval of the variations on 7th April 2014 (PL 00289/1732-1735) and on 8th April 2014 (PL 00289/1736-1739) the PILs were updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.