Public Assessment Report

Decentralised Procedure

VANQUORAL 10, 25, 50 AND 100 MG CAPSULES, SOFT

(ciclosporin)

UK/H/4128/001-004/DC

UK Licence No:
PL 00289/1404-07

Teva UK Limited
LAY SUMMARY

On 23 May 2013, Bulgaria (25, 50 and 100 mg strengths only), the Czech Republic, Germany, Greece, Italy, Poland, Portugal, Spain (25, 50 and 100 mg strengths only), Slovenia, Slovakia and the UK agreed to grant Marketing Authorisations to Teva UK Limited for the medicinal products Vanquoral 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1404-7; UK/H/4128/001-4/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 Vanquoral 10, 25, 50 and 100 mg Capsules, soft outweigh the risks and Marketing Authorisations were granted.
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### Module 1

**Information about initial procedure**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Vanquoral 10, 25, 50 and 100 mg Capsules, soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Form</td>
<td>Soft capsules</td>
</tr>
<tr>
<td>Strength</td>
<td>10 mg, 25 mg, 50 mg and 100 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Teva UK Limited</td>
</tr>
<tr>
<td></td>
<td>Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>UK/H/4128/001-4/DC: The Czech Republic, Germany, Greece, Italy, Poland, Portugal, Slovenia and Slovakia UK/H/4128/002-4/DC: The Czech Republic, Germany, Greece, Italy, Poland, Portugal, Slovenia, Slovakia, Bulgaria and Spain</td>
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<tr>
<td>Procedure Number</td>
<td>UK/H/4128/001-4/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 23 May 2013</td>
</tr>
</tbody>
</table>
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 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 example of label text for the product licence PL 00289/1404. The label texts for PL 00289/1405-7 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

Vanquoral 10 mg Capsules, soft
ciclosporin

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

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1. **NAME OF THE MEDICINAL PRODUCT**

Vanquoral 10 mg Capsules, soft
cyclosporin

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2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each soft capsule contains 10 mg cyclosporin.

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3. **LIST OF EXCIPIENTS**

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

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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

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5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

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

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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.

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7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

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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 00289/1404

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Vanquoral 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 Vanquoral 10, 25, 50 and 100 mg Capsules, soft (PL 00289/1404-7; UK/H/4128/001-4/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Bulgaria (25, 50 and 100 mg strengths only), the Czech Republic, Germany, Greece, Italy, Poland, Portugal, Spain (25, 50 and 100 mg strengths only), Slovenia, Slovakia as Concerned Member States (CMS).

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 the German version of the innovator product, Sandimmun Optoral 100 mg Weichkapseln (Novartis Pharma GmbH, Germany).

Vanquoral 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). Vanquoral 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 Vanquoral 100 mg Capsules, soft (the test product) with Sandimmun Optoral 100 mg Weichkapseln (the German version of 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.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Vanquoral 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 (ATC code)</td>
<td>Immunosuppressive agents, calcineurin inhibitors (L04AD01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Soft capsules 10 mg, 25 mg, 50 mg and 100 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4128/001-4/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>UK</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/4128/001/DC: The Czech Republic, Germany, Greece, Italy, Poland, Portugal, Slovenia and Slovakia UK/H/4128/002-4/DC: The Czech Republic, Germany, Greece, Italy, Poland, Portugal, Slovenia, Slovakia, Bulgaria and Spain</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/1404-07</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Teva UK Limited Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Ciclosporin

rINN: Ciclosporin


Structure:

Molecular formula: C₆₂H₁₁₁N₁₁O₁₂
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 monolinoelate, 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 Vanquoral 100 mg Capsules, soft (the test product) with Sandimmun Optoral 100 mg Weichkapseln (the German version of the reference product) under both fed and fasting conditions.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, 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 these products 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) forms
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, Vanquoral 100 mg Soft Gelatin Capsules (Teva Czech Industries) with the German 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:
Compared with the reference product, the 90 % confidence intervals for the test product (A versus B) are within 90.00-111.11 % for C\textsubscript{max} 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, Vanquoral 100 mg Soft Gelatin Capsules (Teva Czech Industries) with the German 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:
**Overall bioequivalence study conclusion**
Vanquoral 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 *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1), 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, 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 Vanquoral 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 Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), 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, 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2014</td>
<td>IB</td>
<td>To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.1 of the SmPC in accordance with the outcome of an Article 30 referral procedure for the reference product Neoral Soft Gelatin Capsules. Consequently, the PIL has been updated.</td>
<td>Approved 08/04/14</td>
</tr>
</tbody>
</table>
Annex 1

Reference: PL 00289/1404 – 0003
            PL 00289/1405 – 0003
            PL 00289/1406 – 0003
            PL 00289/1407 – 0003

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

Marketing Authorisation Holder: Teva UK Limited
Active Ingredient(s): Ciclosporin

Reason:
To update sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.1 of the Summary of Product Characteristics (SmPC) in accordance with the outcome of an Article 30 referral procedure for the reference product Neoral Soft Gelatin Capsules. Consequently, the Patient Information Leaflet (PIL) has been updated.

Supporting Evidence
Revised SmPC fragments and a revised PIL have been provided. The currently approved labelling is acceptable and needs no further revisions.

Evaluation
The amended sections of the SmPC and the amended PIL are satisfactory.

The current approved UK versions of the SmPC and PIL for these products are available on the MHRA website.

Decision
Approved on 08 April 2014.