COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules

(ciclosporin)

NL/H/4215/001-004/DC

Date: 26 August 2019

This module reflects the scientific discussion for the approval of Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules. The procedure was finalised at 11 March 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for of Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules, from Sandoz B.V.

The product is indicated for:

Transplantation indications

- *Solid organ transplantation*
  Prevention of graft rejection following solid organ transplantation.

- Treatment of transplant cellular rejection in patients previously receiving other immunosuppressive agents.

- *Bone marrow transplantation*
  Prevention of graft rejection following allogeneic bone marrow and stem cell transplantation.

- Prevention or treatment of graft-versus-host disease (GVHD).

Non-transplantation indications

- *Endogenous uveitis*
  Treatment of sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients in whom conventional therapy has failed or caused unacceptable side effects.

- Treatment of Behçet uveitis with repeated inflammatory attacks involving the retina in patients without neurological manifestations.

- *Nephrotic syndrome*
  Steroid-dependent and steroid-resistant nephrotic syndrome, due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.
  It can be used to induce and maintain remissions or to maintain steroid-induced remission, allowing withdrawal of steroids.

- *Rheumatoid arthritis*
  Treatment of severe, active rheumatoid arthritis.

- *Psoriasis*
  Treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.

- *Atopic dermatitis*
  The product is indicated in patients with severe atopic dermatitis when systemic therapy is required.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sandimmun Neoral 10 mg, 25 mg, 50 mg, 100 mg soft capsules which were first registered in Germany in February 1993 (25 mg, 50 mg and 100 mg strengths) and June 1998 (10 mg strength). In the Netherlands, Neoral 10 mg, 25 mg and 100 mg, capsules have been registered by Novartis Pharma B.V. since 9 November 1994 (25 mg and 100 mg strengths) and 24 August 1998 (10 mg strength) via the procedure DE/H/4019.

The MAH included a statement of identity declaring that Menelri soft capsules are qualitatively and quantitatively identical to Sandimmun Neoral soft capsules.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Denmark, France, Romania, Sweden and the United Kingdom. In addition, for the three highest strengths Czech Republic, Estonia, Latvia, Lithuania and the Slovak Republic were CMS.

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

II. QUALITY ASPECTS

II.1 Introduction

- Menelri 10 mg is a yellow-white oval shaped soft gelatin capsule, imprinted with “NVR 10” in red. Each capsule contains 10 mg ciclosporin.
- Menelri 25 mg is a blue-grey oval shaped soft gelatin capsule, imprinted with “NVR 25mg” in red. Each capsule contains 25 mg ciclosporin.
- Menelri 50 mg is a yellow-white oblong shaped soft gelatin capsule and imprinted with “NVR 50mg” in red. Each capsule contains 50 mg ciclosporin.
- Menelri 100 mg is a blue-grey oblong shaped soft gelatin capsule, imprinted with “NVR 100mg” in red. Each capsule contains 100 mg ciclosporin.

The soft capsules are packed in PA/Alu/PVC-Alu blister packs of double-sided aluminium consisting of an aluminium foil on the bottom side and an aluminium foil on the upper side.

The excipients are:

Capsule content - all-rac-alphatocopherol, ethanol anhydrous, propylene glycol, maize oil-mono-di-triglycerides and macrogolglycerol hydroxystearate.
Capsule shell – titanium dioxide (E171), glycerol 85%, propylene glycol and gelatin. The 25 mg and 100 mg capsule contain additionally black iron oxide (E172).
Imprint - carminic acid (E120), aluminium chloride hexahydrate, sodium hydroxide, propylene glycol and hypromellose type 2910.

II.2 Drug Substance

The active substance is ciclosporin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white, finely crystalline powder. Ciclosporin exhibits polymorphism and the tetragonal form is used in manufacturing of the drug product. Ciclosporin is practically insoluble in water, freely soluble in anhydrous ethanol and methylene chloride. All carbon atoms in α-position to the peptide bonds have the absolute L configuration, except one of the alanyl moiety, which is D, and that of the N-methylglycyl subunit, which is achiral. The pH of a solution of ciclosporin drug substance with concentration of 0.2 g/L at 20°C is in the range of 6.5 to 7.

Full information on the synthesis, control and stability of the active substance has been provided. The information is the same as for the similar, authorised, innovator product.

Manufacturing process
Ciclosporin is isolated from a fermentation process with Tolypocladium inflatum gams (*Trichoderma polysporum*) species. The isolation of crude ciclosporin is followed by several purification steps of chromatography and crystallisation. No additional chemical transformations are performed. There are no aseptic or sterilisation processes included in the manufacture of ciclosporin drug substance. The raw materials (solvents, reagents and auxiliary materials e.g. catalysts) used in the synthesis of ciclosporin are commercially available or were prepared from commercially available materials. No Class I solvents or catalysts are used in the synthesis.

Quality control of drug substance
The active substance specification and methods are in line with the Ph. Eur. Monograph, with some tighter limits and some additional tests (residual solvents, heavy metals, microbial quality). The additional methods have adequately been described and where applicable, also validated. Results of batch analysis of three production batches have been provided. The results comply and are consistent.

Stability of drug substance
Stability data on the active substance have been provided, including results of three full scale batches stored at 25°C/60% RH (60 months) and 40°C/75%RH (6 months). The batches were stored in a packaging equivalent to the commercial packaging. On basis of the data submitted, a shelf life was granted of three years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form. The products are similar to the existing and authorised innovator product. Specifically, new development studies have not been performed.

Manufacturing process

The process is a straightforward soft gelatin capsules manufacturing process which starts with the preparation of the capsule filling solution and the preparation of the gelatine capsule mixture, and subsequent the encapsulation is performed under drying. The manufacturing process and in-process controls are adequately described. Results of validation of the manufacturing of soft gelatin capsules of all four strengths at commercial scale have been included.

Control of excipients

The excipients comply with Ph. Eur. and in-house requirements. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance of the shell and the contents, identification and assay of ciclosporin, ethanol, propylene glycol, and tocopherol, identification of the colorants, appearance in water, droplet size, disintegration, dissolution, degradation products, uniformity of dosage units by content uniformity and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of all strengths from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for multiple batches stored at long-term, intermediate and accelerated conditions in accordance with applicable European guidelines.
On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'The product may be stored at room temperature not exceeding 25°C. Increases in temperatures up to 30°C for a total maximum of 3 months do not affect the quality of the product. Store in the original package in order to protect from moisture'. The product should be left in the blister pack until required for use. When a blister is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsule.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Menelri has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Menelri is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sandimmun Neoral which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ciclosporin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH of the reference product has submitted an identity statement that the products under review here, Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules, and the reference (innovator) product Sandimmun Neoral are identical. Hence Menelri is produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as their currently manufactured reference product. As the member states have been ensured that Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules are identical to the reference product Sandimmun Neoral, a biowaiver has been granted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Menelri.

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

Important identified risks	• Lymphomas and other malignancies (including skin malignancies following excessive ultraviolet radiation exposure)
Important potential risks	• Reproductive toxicity
Missing information	• Use in children under 16 years of age for nontransplant indications other than nephrotic syndrome

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sandimmun Neoral. No new clinical studies were conducted. The MAH of the reference product demonstrated through an identity statement that Menelri is identical to the reference product. Therefore bioequivalence testing is not required. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Sandimmun Neoral 10 mg, 25 mg, 50 mg, 100 mg soft capsules. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Menelri 10 mg, 25 mg, 50 mg and 100 mg, soft capsules has a proven chemical-pharmaceutical quality and are generic forms of Sandimmun Neoral 10 mg, 25 mg, 50 mg, 100 mg soft capsules. Sandimmun Neoral is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product has the same quantitative and qualitative composition as Sandimmun Neoral and is produced in the same manufacturing site.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Menelri with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 March 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4215 /IA/001/G	– Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing – Change in the specification parameters and/or limits of an excipient; tightening of specification limits	Yes	04-08-2019	Approved	-