



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2013
EMA/589501/2013

Assessment report for Sandimmun Neoral and associated names

Procedure under Article 30 of Directive 2001/83/EC

INN of the active substance: Ciclosporin

Procedure no: EMEA/H/A-30/1300

Assessment Report as adopted by CHMP with all the information of a confidential nature deleted.



Table of contents

Table of contents	2
1. Background information on the procedure	3
1.1. Background information on the basis of the grounds for referral.....	3
2. Scientific discussion during the referral procedure	3
2.1. Introduction.....	3
2.2. Critical Evaluation: clinical aspects	4
2.3. Recommendation	27
2.4. Conclusions	28

1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 15 December 2011 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products:

Sandimmun Neoral and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the December 2011 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Tomas Salmonson as rapporteur and Dr Romaldas Maciulaitis as co-rapporteur.

In December 2012 the rapporteurship was transferred to Dr Kristina Dunder.

Sandimmun Neoral medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

Sandimmun Neoral is a microemulsified formulation of ciclosporin. Ciclosporin is a cyclic polypeptide consisting of 11 amino acids, which blocks the resting lymphocytes in the G0 or G1 phase of the cell cycle and also inhibits the production and release of cytokines, including interleukin-2. It is a potent immunosuppressive agent. Ciclosporin is used in human solid organ and bone marrow transplantation to prevent graft rejection and in Graft Versus Host Disease (GVHD). Ciclosporin is also used in a variety of conditions that are known, or may be considered, to be of autoimmune origin (endogenous uveitis, nephrotic syndrome, rheumatoid arthritis, psoriasis and atopic dermatitis).

In comparison to Sandimmun (oil-based formulation of ciclosporin), Sandimmun Neoral (microemulsified formulation) provides improved dose linearity of ciclosporin exposure, a more consistent absorption profile and shows less influence from concomitant food intake and from diurnal rhythm. Overall, these properties result in lower within-patient variability in the pharmacokinetics of ciclosporin and a stronger correlation between trough concentrations and total exposure (AUC). As a consequence of these additional advantages, Sandimmun Neoral can be administered independently of mealtimes. In addition, Sandimmun Neoral produces a more uniform exposure to ciclosporin throughout the day and from day to day on a maintenance regimen.

Sandimmun Neoral was first registered in Germany in February 1993 and is available in the EU as 10 mg, 25 mg, 50 mg, 100 mg soft gelatin capsules and 100 mg/ml oral solution. The registration of Sandimmun Neoral was based on efficacy and safety data from clinical studies performed with the oil-based formulation (Sandimmun), first registered in Switzerland in December 1982. Additional pharmacokinetics and pharmacodynamics studies, as well as non-clinical trials were performed with Sandimmun Neoral medicinal product to support its registration.

In the European Union (EU), Sandimmun and Sandimmun Neoral are registered via national procedures. Sandimmun Neoral is available as Sandimmun Neoral soft gelatin capsules (10 mg, 25 mg, 50 mg and 100 mg) and Sandimmun Neoral oral solution, 100 mg/ml. Sandimmun is available as Sandimmun soft gelatin capsules (25 mg, 50 mg and 100 mg), Sandimmun oral solution, 100 mg/ml and Sandimmun concentrate for solution for infusion, 50mg/ml.

Not all strengths and pharmaceutical forms are registered in each country. Furthermore, not all indications are approved in each country. The cumulative sales data for Sandimmun/Sandimmun Neoral is accessible only from 1993 onwards. The total exposure from 1993 on the basis of the sales

data is estimated to approximate 4.9 million patient-years (PSUR 13 covering the period from 01 January 2007 to 31 December 2009).

In October 2010, Sandimmun Neoral was included in the list of products for Summary of Product Characteristics (SmPC) harmonization, requested by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC. Due to the divergent national decisions taken by Member States (MS) concerning the authorization of Sandimmun Neoral (and associated names), the European Commission (EC) notified the EMA/CHMP secretariat of an official referral under Article 30(2) of Directive 2001/83/EC, to resolve divergences amongst the nationally authorised Sandimmun Neoral SmPCs across the EU/EEA region. A pre-referral meeting was held on 12 July 2011 between the European Medicine Agency and the MAH. At the CHMP-meeting of December 2011, the CHMP issued a list of questions with issues to be addressed related to essentially all parts of the SmPC.

To achieve a harmonized SmPC, the MAH used the wording that is common to national SmPCs in the majority of MSs and the Novartis Core Data Sheet (CDS) for Sandimmun Neoral (dated 13 February 2012), based on review of submitted legacy studies and literature references was also used. The agreed Core Safety profile (CSP) from the last PSUR 13 work sharing procedure (EE/H/PSUR/0007/001) and the public AR from the paediatric article 45 procedure (CZ/W/04/pdWS/01, 2010) were used.

2.2. Critical Evaluation: clinical aspects

In general, the MAH proposed a harmonised text drafted mainly using as basis the wording that is common to national SmPCs in the majority of MSs with some amendments reflecting the following:

- the MAH's CDS dated 13 February 2012, as justified by a review of submitted legacy studies, and identified literature references;
- the agreed CSP, from the last PSUR 13 work sharing procedure (EE/H/PSUR/0007/001), where all the EU countries have submitted variation applications to update their national label with the agreed CSP information.

The product information (PI) was presented using the latest version of the QRD template, version 2, published on 12 October 2011.

During the evaluation process, the proposed PI for each pharmaceutical form has been presented in one document using grey-shaded text to differentiate the proposed wording pertaining to one specific dosage. The text without shading in the proposed PI is applicable to all dosage forms. Sandimmun Neoral 10 mg, 25 mg, 50 mg and 100 mg soft gelatin capsules have therefore been combined.

Accordingly, the following grey-shading code is used in the proposed harmonized Product Information:

- Sandimmun Neoral and associated names (see Annex I) 10 mg soft capsules
- Sandimmun Neoral and associated names (see Annex I) 25 mg soft capsules
- Sandimmun Neoral and associated names (see Annex I) 50 mg soft capsules
- Sandimmun Neoral and associated names (see Annex I) 100 mg soft capsules

There is no grey-shading code for Sandimmun Neoral oral solution as there is only one dosage: 100 mg/ml.

A number of areas of disharmony in the Product Information have been considered as follows:

Section 4.1 – Therapeutic indications

This section differs to a varying extent between EU member states. The main discrepancies are mentioned below. Not all MS have the following therapeutic indications:

- Bone marrow transplantation;
- Treatment of transplant rejection in patients receiving other immunosuppressive agents;
- Prevention/treatment of graft versus host disease;
- Steroid resistant nephrotic syndrome;
- Endogenous uveitis;
- Acquired severe bone marrow aplasia.

Transplantation indications

- *Solid organ transplantation:*

In line with the overall Marketing Authorization Holder's (MAH) strategy to propose a harmonized SmPC label using as the basis the most commonly approved wording in EU member states as well as the most recently updated version of the company CDS dated 13 February 2012, the MAH proposed an indication wording which is already approved as proposed in 21 EU national labels, using the following wording:

"Prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic transplantations.

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

The CHMP questioned the MAH's justification with regards to the listing of specific organ transplantations in the indication instead of stating "*Solid organ transplantation*". In this respect, the CHMP also requested the MAH to clarify if there are specific organ transplantations for which ciclosporin is not appropriate to use.

The MAH agreed with the CHMP that no specific organ transplantations should be mentioned in section 4.1 unless there are ones that are not appropriate to use, leading to the following agreed wording:

"Prevention of graft rejection following ~~kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic~~ solid organ transplantation."

With regards to the treatment of rejection, the CHMP considered that the indication "*Treatment of transplant rejection in patients previously receiving other immunosuppressive agents*" was not specific enough encountering also the use of the product in case of controversial conditions, namely, in case of humoral rejection, after tacrolimus therapy, in case of chronic allograft injury. The main concerns reflected by the CHMP in this question related to the switch from tacrolimus, treatment of humoral rejections with ciclosporin and in case of chronic allograft injury, as this has been seen as chronic rejection. In all of these cases the ciclosporin use was questioned by the CHMP.

The vast majority of transplant patients receive an immunosuppressive regimen that includes one of the only two calcineurin inhibitors (CNI): ciclosporin or tacrolimus. The MAH considered that restricting the possibility to switch from one agent to the other (due to lack of efficacy or for safety reasons) as suggested, is detrimental to the optimal treatment of transplant patients and the choice should remain for physicians to switch from one to the other CNI. This position is acknowledged in the European label of the other CNI, tacrolimus which allows for switching from ciclosporin to tacrolimus as an option for the treatment of rejection. Therefore the MAH insisted in maintaining the possibility to switch from other immunosuppressive agents, e.g. tacrolimus. Although the common practice would be to change to another agent in case of rejection, underlying data supporting efficacy of ciclosporin in case of rejection with tacrolimus or other immunosuppressive agents was lacking in the submission data; thus, the CHMP requested the MAH to compile all available data on switch to ciclosporin in case of rejection with any other immunosuppressive agent, not only tacrolimus. In response to this question, the MAH described some scenarios, e.g. conversion from tacrolimus to ciclosporin in renal transplant patients for management of new onset post-transplant diabetes mellitus without increased risk of rejection or in liver transplant patients with hepatitis C infections. The CHMP agrees with the MAH that maintenance of immunosuppressive treatment in transplantation include administration of drugs from the various groups of immunosuppressive agents and that conversion to a different drug and/or combination often occurs for safety and/or efficacy reasons. Thus, the common practice is to change to another agent in case of rejection.

The inclusion of the term "*cellular*" rejection was also discussed since the diagnosis of humoral rejection episodes is controversial. The 1997- 2009 update Banff classification of renal transplant pathology categorises episodes of acute rejection not only in the two main groups: T-cell mediated rejection and antibody mediated changes, but includes a third category of "borderline changes". Therefore, the MAH considers that restricting of the use of ciclosporin to patients with acute "*cellular*" rejection, may affect optimization of outcomes of a substantial number of patients, especially those with "borderline" changes who may benefit with the option of the administration of one CNI or another depending on their immunologic or safety risks. Therefore the MAH accepts that introducing Sandimmun Neoral for the treatment of rejection might be the most appropriate for cellular rather than humoral rejection, based on the mechanism of action of CNI's.

The final below wording was agreed accordingly:

*“Prevention of graft rejection following solid organ transplantation.
Treatment of transplant cellular rejection in patients previously receiving other immunosuppressive agents”.*

- *Bone marrow transplantation (BMT)*

All MS except Norway have the indication bone marrow transplantation and GVHD approved. The MAH's proposed indication wording for the bone marrow transplantation is approved in 23 EU countries. Some wording differences exist among the remaining countries and the MAH has reviewed the national labels of these 6 EU countries where currently approved indication wording deviate from the proposed harmonized SmPC. The MAH proposed the following wording for this indication:

“Prevention of graft rejection following bone marrow transplantation.

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

The efficacy of ciclosporin has been demonstrated in bone marrow transplant (BMT) recipients in eight studies carried out in Europe and US with a total of 227 patients. Seven trials were conducted for the prevention of graft-versus host disease (GVHD), one trial for the treatment of acute GVHD. Five European centers (EU 1-5) and one U.S. center (US 6) conducted “open” non-randomized trials for the prevention of GVHD. One randomized trial (US 3) was conducted for the prevention of GVHD and one randomized trial (US 11) was conducted for the treatment of acute GVHD. Six patients in US received ciclosporin in an effort to reverse established acute, severe (Grade III-IV) GVHD. These patients had not been previously treated with ciclosporin and the GVHD was resistant to other therapies. Results from these studies were compared to methotrexate (MTX) therapy in the prevention of GVHD trials (historical controls in the open trials) and to steroid therapy in the treatment of GVHD trial. These studies contained 227 patients: 204 patients were BMT recipients treated for prophylaxis of GVHD, and 23 patients treated for established GVHD. There were a total of 20 HLA mismatched patients in these studies (Ringden, Olle 1985).

The MAH is of the view that the efficacy of ciclosporin in bone marrow transplantation and GVHD is well established from the data in the original MAA, published clinical studies and extensive clinical use.

The CHMP questioned though the benefit-risk of ciclosporin *in “prevention of graft rejection following bone marrow transplantation”*: the CHMP requested the MAH to submit data confirming a positive benefit-risk of ciclosporin in terms of frequency of stem cell engrafting/graft failure (i.e. outcomes different than the frequency of GVHD episodes) beyond the benefits/risk (B/R) of conditioning treatment (HD cyclophosphamide/busulfan and/or TBI). In addition, a clarification of the B/R of ciclosporin in prevention of graft rejection after non-myeloablative stem cell transplantation was also requested by the CHMP.

In their response the MAH referred back to the same studies as in the initial response. The main focus of these studies was, however, on the development of GVHD, although patient survival and time to engraftment were assessed (no data on time to engraftment in some studies). The studies showed that the proportion of and time to engraftment for ciclosporin was similar or in some studies better than that of controls. Patient survival at 1 year differed across studies, ranging from 38 to 89%. Despite the fact that these open-label studies were small and mostly non-randomized, as stated by the MAH, BMT and Graft versus Host Disease (GVHD) are rare conditions and the data from these studies as well as extensive clinical experience are supportive of the indication *“Prevention of graft rejection”* for ciclosporin. The CHMP is in agreement with the MAH's position.

A clarification of the B/R of ciclosporin in prevention of graft rejection after non-myeloablative stem cell transplantation was also requested by the CHMP. The applicant referred to four publications, involving 179 patients and describing different modalities of non-myeloablative stem cell transplants. Ciclosporin was used as concomitant medication for prevention of GVHD. These studies did not compare ciclosporin with other drugs, however, they show that ciclosporin may be used in this context and provide experience with the use of ciclosporin in this indication. Although data is limited in non-myeloablative stem cell transplantation, the CHMP is of the view that it is not considered necessary to specify myeloablative vs. non-myeloablative stem cell transplantation in the ciclosporin indication.

The CHMP also requested the MAH to discuss whether the heading *“bone marrow transplantation”* shall be updated to *“allogeneous stem cell transplantation”*, i.e. independent from the source (else than non-host) of the stem cells and blasts. The studies in the initially submitted referral dossier refer only to stem cells originated from bone marrow, but the MAH referred to literature data to support that

ciclosporin has been used subsequently in stem cell transplantation regardless of the source of stem cells. This was based mainly on two published studies, none of them with a comparator to ciclosporin. There was limited data from controlled studies to support the use of ciclosporin regardless of the source of stem cells, however, the CHMP is of the view that clinical experience supports the proposed additions in the indication.

The final below wording was agreed accordingly:

"Bone marrow transplantation

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

Prevention of graft versus host disease (GVHD)."

Non-transplantation indications

Endogenous uveitis

The MAH proposed the following wording for this indication:

"Treatment of active 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."

The MAH's proposed indication wording for the uveitis and Behçet uveitis is approved in 14 EU countries. The MAH has reviewed the national labels of the 10 EU countries where currently approved indication wording deviate from the proposed harmonized SmPC. In 5 EU countries, endogenous uveitis, including Behçet's uveitis is not approved.

The review of the original Sandimmun Dossiers from major markets such as France, the U.S. and UK which contains the clinical results from a total of 15 global studies (see table below) has been performed. The dossier of Sandimmun was used as a basis of the review as the dossier supporting the approval of the new ciclosporin formulation (Sandimmun Neoral) was based on pharmacokinetics evaluation that demonstrated equivalence between the 2 forms of ciclosporin (oil-based formulation versus microemulsified formulation).

The studies presented at renewals of marketing authorization in EU were also screened and reviewed.

At the time of the submission of the oil-based formulation of ciclosporin, Sandimmun, in 1987, a comprehensive clinical data summary on endogenous uveitis was available (Nussenblatt 1987). Two types of studies, open and controlled masked, were carried out in order to evaluate the efficacy of ciclosporin in the treatment of severe sight-threatening intermediate and posterior uveitis. Details of studies 1-15, included in the initial approval, are reported in (Nussenblatt 1987).

Table 1: List of clinical studies from the submission

Study Code	Study title	Compound	Type of study
1	The Turkish pilot study in Behçet's disease with ocular involvement	Ciclosporin oil-based	Pilot, uncontrolled study
2	The French pilot study in uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
3	The French study in birdshot chorioretinopathy	Ciclosporin oil-based	Pilot, uncontrolled study
4	The Danish pilot study in uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
5	The British two-centre pilot study in uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
6	The American long term study in uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
7	The Japanese multicentre pilot study in Behçet's disease with ocular involvement	Ciclosporin oil-based	Pilot, uncontrolled study
8	The Israeli study in refractory uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
9	The Saudi Arabian low dose study in Behçet's disease with ocular involvement	Ciclosporin oil-based	Pilot, uncontrolled study
10	The Italian multicentre low-dose study in uveitis	Ciclosporin oil-based	Pilot, uncontrolled study
11	The Egyptian low-dose study in Behçet's disease with ocular involvement	Ciclosporin oil-based	Pilot, uncontrolled study
12	The American controlled study in uveitis vs. prednisolone	Ciclosporin oil-based vs. prednisolone	Randomized, comparative study
13	The Japanese controlled multicentre study in Behçet's disease vs. colchicine	Ciclosporin oil-based vs. colchicine	Randomized, comparative study
14	The Israeli controlled study in Behçet's disease with ocular involvement vs. conventional treatment	Ciclosporin oil-based vs. prednisone, chlorambucil	Randomized, comparative study
15	The Dutch controlled multicentre study in uveitis vs. placebo	Ciclosporin oil-based vs. placebo	Randomized, comparative study

The CHMP was of the view that the data provided by the MAH to support these indications are rather scarce. In addition clinical trials examining efficacy of ciclosporin in treatment of endogenous uveitis were small and lack of power to show statistically significant results. Hence the CHMP questioned the benefit-risk balance of ciclosporin in treatment of endogenous uveitis and Behçet's uveitis.

Despite scarcity of data the CHMP noted that the majority of patients benefited from ciclosporin treatment in all reports. Although some patients experienced adverse reactions, mostly nephrotoxicity, hypertension and metabolic disorders, the CHMP noted that these adverse reactions are well known and could be managed in dose dependent manner.

From the data provided and other published data the CHMP concluded that benefit-risk ratio for ciclosporin in treatment of endogenous refractory uveitis, including Behçet uveitis, is positive. However, the MAH was requested to address whether ciclosporin should be used as monotherapy or in combination with other medicines such as corticosteroids.

In response to this request the MAH provided data which was included in the original submission (1988) dossier and assessment that low dose systemic corticosteroids may be given concomitantly for control of the inflammatory process in the eye. Furthermore, in cases of sight-threatening intermediate and posterior uveitis, especially in Behçet's disease, the MAH clarified that ciclosporin in combination with low dose systemic corticosteroid if necessary could be used in order to achieve remission. Therefore, the MAH considers that there is data to support the administration of ciclosporin alone or in combination with steroids depending of the severity of the disease and according to the physician assessment of the patient tolerability, and that the previously proposed wording in section 4.2: "*... To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Sandimmun Neoral alone does not control the situation sufficiently....*", is adequate.

The MAH responded that ciclosporin can be used alone or in combination with corticosteroids if ciclosporin alone does not control treatment of the uveitis, including Behçet uveitis.

The CHMP also raised questions regarding the risk of aggravation of the neurological manifestations of Behçet's disease by ciclosporin. Neurological manifestations occur in less than one-fifth of patients with Behçet's disease. Based on literature and supportive data the MAH is of the view that the data presented supports the positive benefit/risk of the indication while recommending using ciclosporin as systemic therapy both for non-infectious uveitis and for the ocular manifestations of Behçet's disease in patients without neurological manifestations. The MAH proposes the following wording accordingly in section 4.1:

"Endogenous uveitis

"Treatment of ~~active~~ 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."

The CHMP is in agreement with the above wording proposed MAH and also considers that appropriate information is stated in the SPC section 4.2.

The MAH also considered that the additional following wording in relation to the administration of ciclosporin in patients with Behçet's disease in the section *"Additional Precautions in Endogenous Uveitis"* of Section 4.4 of the SmPC should be included, to address the potential risk of neurological complications:

"Sandimmun Neoral should be administered with caution in patients with neurological Behçet's syndrome. The neurological status of these patients should be carefully monitored.

There is only limited experience with use of Sandimmun Neoral in children with endogenous uveitis".

The CHMP is also in agreement with the above mentioned wording.

- Nephrotic syndrome (NS)

The MAH proposed the following wording for this indication:

"Steroid dependent and steroid resistant nephrotic syndrome due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

Sandimmun Neoral can be used to induce and maintain remissions. It can also be used to maintain steroid induced remission, allowing withdrawal of steroids."

The MAH's proposed indication wording for nephrotic syndrome is approved in 16 EU countries. The MAH has reviewed the national labels of the 13 EU countries where currently approved indication wording deviate from the proposed harmonized SmPC.

The efficacy of Sandimmun (oil based formulation of ciclosporin) has been demonstrated in 4 randomized controlled and 5 uncontrolled studies. The clinical results from these 9 clinical studies were analyzed using a pooling of data from all studies (controlled and uncontrolled). To ease the review, two separate sections for controlled and uncontrolled studies are presented. In parallel of these 9 performed studies, 2 double-blind placebo controlled multicenter studies (9515 and 9516) and 1 multicenter study comparing ciclosporin with cyclophosphamide in steroidresistant patients (9508) had to be stopped prematurely because of a lack of suitable patients consenting to receive placebo or a cytostatic agent. Studies OL 9509 (which includes only patients with IgA-nephropathy) and OL JAPFR (within patient assessment—before and after comparison) are not included in the pooled analysis as they respectively differ from the others studies in term of patients' entry criteria and associated assessment.

Pediatric data from controlled and uncontrolled studies were also provided. At the time of submission, patients of 17 years of age maximum qualified as "children".

In view of the above dataset, the CHMP considers that the efficacy of Sandimmun (oil based formulation of ciclosporin) has been demonstrated in 4 randomized controlled and 5 uncontrolled studies as well as studies conducted in pediatric patients. Moreover, recent trials have confirmed the benefit of Sandimmun Neoral in different forms of nephrotic syndrome in children and adults.

However the CHMP has concerns over the fact that current indication is too broad as use in secondary glomerulonephritis is controversial. The CHMP therefore requested the MAH to justify the positive benefit risk for all nephrotic conditions except the primary minimal change glomerulonephritis, primary focal segmental glomerulosclerosis, or primary membranous glomerulonephritis. The CHMP is of the view that the indication should be limited to primary glomerulonephritis cases as specified above. The below wording was agreed:

“Steroid dependent and steroid resistant nephrotic syndrome due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

Sandimmun Neoral can be used to induce and maintain remissions. It can also be used to maintain steroid induced remission, allowing withdrawal of steroids.”

- *Rheumatoid arthritis (RA)*

The MAH proposed the following wording for this indication:

“Treatment of severe, active rheumatoid arthritis.”

The MAH's proposed indication wording for rheumatoid arthritis is approved in 13 EU countries. Some wording differences exist among the remaining countries and the MAH has reviewed the national labels of these 16 EU countries where currently approved indication wording deviate from the proposed harmonized SmPC.

The rationale given by the MAH for the proposed indication was based on the following data: the initial pilot study in active rheumatoid arthritis used a dose of 10 mg/kg/day, half the dose used in solid organ transplantation at that time. The promising benefit was offset by the renal dysfunction and hypertension. Subsequent studies using lower doses showed a better risk-benefit ratio. European controlled double-blind trials used 5 mg/kg/d that allowed a downward titration to find the maximum tolerated dose. Renal dysfunction above the critical threshold, defined as creatinine increased by 30-50% over baseline, was less of a problem when starting with a dose of 2.5 mg/kg/day. The control groups were either using placebo, or azathioprine, or D-penicillamine. This data, along with ciclosporin experience in other nontransplant diseases, helped to design the four pivotal placebo-controlled double-blind Sandimmun (SIM) trials in severe RA in the US and Canada.

The MAH presented respectively the clinical efficacy outcome of the US and Canada studies and then the European studies.

Rheumatoid arthritis is an approved therapeutic indication in all EU countries. ciclosporin has been extensively studied in several clinical trials in patients with rheumatoid arthritis in whom conventional therapy is ineffective or inappropriate, as well as in many published studies reporting the use of ciclosporin in this indication. The CHMP is of the opinion that the available data confirms the use of ciclosporin in the following indication: *“Treatment of severe, active rheumatoid arthritis.”*

Wording regarding medical supervision was inserted in Section 4.4 Special warnings and precautions for use accordingly.

- *Psoriasis*

The MAH proposed the following wording for this indication:

“Treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.”

The Psoriasis is an approved therapeutic indication in all EU countries but some deviations from the proposed SmPC text exists in 9 EU states. Based on the comprehensive clinical data summary on psoriasis and references provided by the MAH, the CHMP considers the argumentation made by the MAH acceptable and therefore agrees with the above mentioned wording.

- *Atopic dermatitis*

The MAH proposed the following wording for this indication:

“Sandimmun Neoral is indicated in patients with severe atopic dermatitis when systemic therapy is required.”

The MAH's proposed indication wording for the Atopic dermatitis is approved in 15 EU countries. Some wording differences exist among the remaining countries and the MAH has reviewed the national labels of the EU countries where currently approved indication wording deviate from the proposed harmonized SmPC.

Ciclosporin has been studied in several clinical trials in atopic dermatitis, although the studies by modern standards are considered small. 15 EU countries already have exactly the proposed label and in those which do not, the deviations are not considered large. Therefore, based on clinical data summary on atopic dermatitis and references provided by the MAH, the CHMP considers the argumentation made by the MAH acceptable and therefore agrees with the above mentioned wording.

- *Aplastic Anemia*

The indication aplastic anemia is approved only in France with the following wording:

“Treatment of severe acquired aplastic anemia in patients who are not eligible for bone marrow transplantation.”

As recorded in the July 27th 2011 minutes of the pre-referral meeting regarding the approach to label harmonisation the Agency agreed with the MAH's proposal to use the SmPC wording that is common in the majority of the Member States, the Sandimmun and Neoral CDSs as justified by the review of legacy studies and literature references.

In line with this agreement, the MAH did not include the indication of aplastic anemia in the harmonized label of Sandimmun and Sandimmun Neoral since this indication is approved in only one of 27 member states and is not listed in Sandimmun and Sandimmun Neoral CDSs.

The CHMP endorses this proposal

Section 4.2 – Posology and method of administration

This section contains general parts as well as separate sub-sections for each indication. In the following, the entire section 4.2 is reviewed, sub-section by sub-section.

Posology:

The MAH proposed the following wording for the posology:

“The dose ranges given for oral administration are intended to serve as guidelines only. The daily doses of Neoral should always be given in two divided doses.”

The MAH's statement “The dose ranges given for oral administration are intended to serve as guidelines only” is endorsed by the CHMP. The statement “The daily doses of Neoral should always be given in two divided doses” is partly endorsed by the CHMP since the word “always” should be omitted (in some cases, three times daily administration may be needed).

In addition, the CHMP requested the MAH to specify in the SmPC whether Sandimmun/Sandimmun Neoral should be administered with or without food or if administration may be performed irrespective of concomitant food intake. Considering the narrow therapeutic window for ciclosporin, the CHMP requested the MAH to consider ciclosporin intake in order to reduce intra-individual variability. The MAH acknowledged that food affects the absorption of ciclosporin both from the Sandimmun formulation and, to a lesser extent, from the Sandimmun Neoral formulations. The MAH stated in their response package that the absolute changes may be considered small, but in view of the narrow therapeutic window for ciclosporin, standardized intake in relation to food intake would be preferable to reduce intra-individual variability. The MAH therefore agreed to revise the wording, recommending that Sandimmun Neoral should be administered on a consistent schedule with regard to time of day and relation to meals, as follows:

"The daily doses of Sandimmun/Sandimmun Neoral ~~always~~ should be given in two divided doses equally distributed throughout the day, ~~taken at the same time of the day, e.g., in the morning and in the evening.~~ It is recommended that Sandimmun Neoral be administered on a consistent schedule with regard to time of day and relation to meals. "

This wording is endorsed by the CHMP.

Lastly, based on the fact that ciclosporin is a potent active substance associated with serious safety concerns, the CHMP is of the opinion that the posology section should clearly state that Sandimmun/Sandimmun Neoral is a product to be handled by specialists within the respective therapeutic area; even if this is mentioned in section 4.4, the CHMP considered important to also point this out in section 4.2 and the following general statement should therefore be included as follows:

"Sandimmun/Sandimmun Neoral should only be prescribed by, or in close collaboration with, a physician with experience of immunosuppressive therapy and/or organ transplantation."

The MAH agreed with the above proposed wording and implemented it accordingly.

General monitoring of posology.

The CHMP was of the opinion that a general message about the value of monitoring to guide posology was missing. This type of information is in line with SmPCs of several Member States.

The CHMP was concerned by the fact that different approaches in monitoring proposals for transplantation and non-transplantation populations were proposed by the MAH, ignoring blood levels measurements in non-transplant indications. In response to the CHMP'S request, the MAH adjusted information by adding cautious reference to blood level monitoring options for non-transplant indications and additionally stressing the practice protocols for transplantation indications. This approach was acceptable to the CHMP and final wording were agreed accordingly for the following paragraphs in section 4.2:

- Paragraph on *Non-transplantation indications*, as follows:

"...Occasional monitoring of ciclosporin blood levels may be relevant in non-transplant indications, e.g. when Sandimmun Neoral is co-administered with drugs that may interfere with the pharmacokinetics of ciclosporin, or in case of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction)..."

- - Paragraph on "*Transplantation*", as follows:

"Solid organ transplantation

Treatment with Sandimmun Neoral should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively, ~~before~~ before being gradually reduced in accordance with blood levels according to local immunosuppressive protocols until a recommended maintenance dose ~~of about 2 to 6 mg/kg given in 2 divided doses~~ of about 2 to 6 mg/kg given in 2 divided doses is reached..."

Wordings regarding monitoring were inserted in Section 4.4 accordingly.

Transplantation indications:

The MAH proposed the following wordings for the paragraph on transplantation:

- Solid organ transplantation

Based on the most commonly approved wording in EU member states and the recent version of the company core data sheet (CDS) dated 13 February 2012, the MAH proposed a wording which is already approved in 13 EU MS.

In the original Sandimmun studies, initial doses in the range 14-18 mg/kg/day have been used and these were subsequently reduced to a maintenance dose in the range 6-10 mg/kg/day. The administration started within 2-20 hours prior to surgery. Based on the higher C_{max} and AUC values achieved with Sandimmun Neoral compared to Sandimmun, the resulting individualized doses of

Sandimmun Neoral were on average lower compared to Sandimmun. Hence, this supports the lower doses proposed for Sandimmun Neoral in the proposed SmPC.

The studies in the original Sandimmun dossier are old and the posology based on those data is therefore somewhat obsolete in comparison with the different transplantation regimens used today. The dosage should also be guided by monitoring of ciclosporin blood levels.

In conclusion, the proposed posology in the solid organ transplantation indication was partly acceptable to the CHMP which proposed the following revised wording accordingly:

Treatment with Sandimmun Neoral should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively ~~before~~ being gradually reduced in accordance with blood levels according to local immunosuppressive protocols until a recommended maintenance dose of about 2 to 6 mg/kg given in 2 divided doses is reached.

When Sandimmun Neoral is given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple drug therapy), lower doses (e.g. 3 to 6 mg/kg given in 2 divided doses for the initial treatment) may be used.

The MAH agreed with these revisions and amended the SmPC accordingly.

- *Bone marrow transplantation*

The MAH proposes a wording which is already approved as proposed in 16 EU national labels:

“The initial dose should be given on the day before transplantation. In most cases, Sandimmun solution for intravenous infusion is preferred for this purpose. The recommended intravenous dose is 3 to 5 mg/kg/day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy with Sandimmun Neoral at daily doses of about 12.5 mg/kg given in 2 divided doses. Maintenance treatment should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by 1 year after transplantation.

If Sandimmun Neoral is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation.

Higher doses of Sandimmun Neoral, or the use of Sandimmun intravenous therapy, may be necessary in the presence of gastrointestinal disturbances which might decrease absorption.

In some patients, GVHD occurs after discontinuation of ciclosporin treatment, but usually responds favourably to re-introduction of therapy. In such cases an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily oral administration of the maintenance dose previously found to be satisfactory. Low doses of Sandimmun Neoral should be used to treat mild, chronic GVHD.”

The dosages used in clinical studies that supported the approval of Sandimmun and Sandimmun Neoral in the bone marrow transplant indications were provided by the MAH.

Eight studies evaluating Sandimmun/Sandimmun Neoral in BMT recipients were carried out in a total of 227 patients; seven trials were conducted for the prevention of graft-versus host disease (GVHD) and one trial for the treatment of acute GVHD.

The dosage of ciclosporin varied in the different studies. For prevention of GVHD the usual dosage was 12.5 mg/kg/day. However, several European centers started higher (20-25 mg/kg/day) during the first few days then tapered to 12.5 mg/kg/day. Most centers held the dose constant and tapered after several months, usually discontinuing after 4-6 months. The dosage of ciclosporin used for treatment of GVHD was approximately 15 mg/kg/day. This was tapered over time and discontinued at about 6 months. ciclosporin was given mostly once or twice daily, but at one center, three times daily. In most studies, if the I.V. formulation of ciclosporin was used, it was given at about 1/3 the oral dose. Several of the studies supporting the indication used a higher initial dose (20-25 mg/kg/day by i.m.) during the first few days and then tapered to 12.5 mg/kg/day, however, other studies used an initial oral dose of 12.5 mg/kg/day. The oral bioavailability of approximately 30% supports that the i.v. dose used is about 1/3 of the oral, Sandimmun Neoral dose.

Moreover, the currently approved labels contain recommendations in case of temporary gastrointestinal problems that might interfere with the absorption of orally administered cyclosporine and require replacement using an intravenous infusion. This is considered covered with the proposed wording; the CHMP agrees with this approach.

Furthermore, the labels do not include the wording that if GVHD occurs after discontinuation of ciclosporin treatment, it usually responds favourably to re-introduction of therapy and that low doses of Neoral should be used to treat mild, chronic GVHD. The MAH considers that this information is important for the prescribing physician to optimize the patients' treatment and this is endorsed by the CHMP.

Finally the MAH considers that details regarding kinetics are described in sections 5.1 and 5.2 and therefore not deemed necessary in Section 4.2 of the proposed SmPC, which is agreed by the CHMP. In conclusion, the proposed posology in the bone marrow transplantation indication as approved in 16 EU MS is acceptable to the CHMP.

Non-transplantation indications:

The MAH proposed a new general wording to introduce the paragraph on non-transplantation indications, as general recommendations. The CHMP agrees that general information applicable to all these indications was relevant to include. However the CHMP considers that this paragraph should be complemented with recommendations for further controls to be made, e.g. of liver function, bilirubin, serum electrolytes and blood pressure and that it is preferred to use glomerular filtration rate determined by a reliable and reproducible method rather than serum creatinine. Furthermore, the CHMP is of the view that occasional monitoring of ciclosporin blood levels could be relevant also in these indications, e.g. at initiation of ciclosporin therapy and when ciclosporin is co-administered with drugs that may interfere with the pharmacokinetics of ciclosporin. The MAH was requested to propose a wording accordingly, to include these recommendations. Finally the original MAH's proposed wording included the following statement *"The only accepted route of administration is by mouth (the concentrate for intravenous infusion must not be used)."* The CHMP requested the MAH to justify this statement.

The MAH provided a revised wording in which, as requested by the CHMP, the recommendations related to monitoring of renal function were strengthened. The MAH accepted to modify the SmPC to include monitoring the changes in renal function by the estimation of the glomerular filtration rate (eGFR) by the MDRD formula and to solely recommend the use of eGFR, leading to the following agreed wording:

"Non-transplantation indications

When using Sandimmun Neoral in any of the established non-transplantation indications, the following general rules should be adhered to:

Before initiation of treatment a reliable baseline level of renal function ~~serum creatinine~~ should be established by at least two measurements. The estimated glomerular filtration rate (eGFR) by the MDRD formula can be used for estimation of renal function in adults and an appropriate formula should be used to assess eGFR in paediatric patients. Since Sandimmun Neoral can impair renal function, it is necessary to assess renal function frequently. ~~If eGFR decreases by and if serum creatinine remains increased to more than 25% below 30% above~~ baseline at more than one measurement, ~~to reduce~~ the dosage of Sandimmun Neoral should be reduced by 25 to 50%. ~~If the eGFR decrease increase~~ from baseline exceeds 35% 50%, further reduction of the dose of Sandimmun Neoral should be considered. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in improving eGFR within one month, Sandimmun Neoral treatment should be discontinued (see section 4.4).

Regular monitoring of blood pressure is required.

The determination of bilirubin and parameters that assess hepatic function are required prior to starting therapy and close monitoring during treatment is recommended. Determinations of serum lipids, potassium, magnesium and uric acid are advisable before treatment and periodically during treatment.

Lastly the MAH recommended oral administration in non-transplantation indications due to lack of data and potential risk for anaphylactic reactions with intravenous use; this was acknowledged by the

CHMP. In a short period, it would be adequate to hold the ciclosporin dosage until oral tolerance is regained. However, in case of a more prolonged inability to use oral ciclosporin, use of IV ciclosporin may be considered, provided that care is taken to administer an adequate IV dose. Thus, the following wording was proposed by the MAH and agreed by the CHMP:

Occasional monitoring of ciclosporin blood levels may be relevant in non-transplant indications, e.g. when Sandimmun Neoral is co-administered with drugs that may interfere with the pharmacokinetics of ciclosporin, or in case of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).

The only accepted route..."

- *Endogenous uveitis:*

A review (Nussenblatt 1987) of 15 clinical studies made the following dosage recommendations:

- The initial dose should be 5 mg/kg/day.
- The dose may be increased to a maximum of 7.0 mg/kg/day if necessary and tolerated and for a limited period of time only.
- Attempts should be made to reduce the dose in the maintenance treatment below 5 mg/kg/day.
- Low dose systemic corticosteroids may be given concomitantly for control of the inflammatory process in the eye.

Ciclosporin is very effective in controlling the intraocular inflammatory process and improving or stabilizing visual acuity when administered at dosages of 5 to 10 mg/kg/day initially and 2 to 7 mg/kg/day for maintenance. At high initial doses it compares favorably to large doses of steroids. It has been found more effective than conventional therapy in many cases of sight-threatening intermediate and posterior uveitis, especially in Behçet's disease with ocular involvement.

Another review by Timonen (1987) was also provided by the MAH.

Based on the documentation submitted by the MAH the dose recommendations seem overall appropriate by the CHMP. However, the MAH has identified the national labels of the 9 EU countries where currently approved wording deviate from the proposed harmonized SmPC which was reviewed. The following wording was proposed:

"For inducing remission, initially 5 mg/kg/day orally given in 2 divided doses are recommended until remission of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose can be increased to 7 mg/kg/day for a limited period.

To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Neoral alone does not control the situation sufficiently.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level, which, during the remission phases, should not exceed 5 mg/kg/day."

The CHMP therefore requested the MAH to submit a text concerning treatment of uveitis in which deviations in the national approved SmPC's is highlighted. The main concern reflected in this question was deviations from the national SmPC. In general, the proposed wording of section 4.2 was acceptable to CHMP. However, the CHMP considers that a proportion of patients are on maintenance steroid treatment at the initiation of ciclosporin treatment in the acute phase and thus tapering of steroids may be needed. The CHMP requested the MAH to discuss this and propose a wording to guide the physician how these situations should be managed.

The MAH responded that the average dose of prednisone was 0.5 mg/kg (assuming a 70 kg patient), ranging from 0.2 to 0.8 mg/kg/day at start of treatment, and that the dose was decreased to an average of 0.4 mg/kg/day by the first month, 0.2 mg/kg/day by month 3 and 0.1 mg/kg/day by 1 year. The MAH also proposed an addition to the SmPC section 4.2 that after 3 months, the dose of corticosteroids may be tapered to the lowest effective dose; the CHMP agrees with this proposal. Moreover, the MAH also proposed to include those infectious causes of uveitis should be ruled out before immunosuppressants can be used as therapy; this addition is endorsed by the CHMP.

The following wording was therefore agreed:

“...To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Sandimmun Neoral alone does not control the situation sufficiently. After 3 months, the dose of corticosteroids may be tapered to the lowest effective dose.”

For maintenance treatment, the dose should be slowly reduced to the lowest effective level. During the remission phases, this should not exceed 5 mg/kg/day.

Infectious causes of uveitis should be ruled out before immunosuppressants can be used.”

- *Nephrotic syndrome:*

The MAH proposed dosage and administration wording w already approved in 20 EU national labels. Deviations of the text in 9 countries have been thoroughly discussed by the MAH. The harmonised suggestion of section 4.2 text of the SmPC proposed by the MAH was overall supported by the CHMP with the exception to the time to improvement in case of nephrotic syndrome.

The main concern of the CHMP was not to limit time of 3 months for efficacy assessment in case of nephrotic syndrome but rather to reflect the reported time frame of 3 to 6 months, depending on the type of glomerulopathy. The MAH agreed to update the section accordingly:

“Time to improvement varies from 3 to 6 months depending on the type of glomerulopathy. If no improvement has been observed after time to improvement period, Sandimmun Neoral therapy should be discontinued”.

- Rheumatoid arthritis (RA)

“For the first 6 weeks of treatment the recommended dose is 3 mg/kg/day orally given in 2 divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 5 mg/kg. To achieve full effectiveness, up to 12 weeks of Sandimmun Neoral therapy may be required.

For maintenance treatment the dose has to be titrated individually to the lowest effective level according to tolerability.

Sandimmun Neoral can be given in combination with low-dose corticosteroids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) (see section 4.4). Sandimmun Neoral can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using 2.5 mg/kg Sandimmun Neoral in 2 divided doses per day initially, with the option to increase the dose as tolerability permits.”

A dosage and administration wording is proposed, as already approved in 19 EU national labels. The CHMP noted though that 17 of these countries do not contain the following (underlined) text that is being proposed for harmonized label: *“For maintenance treatment the dose has to be titrated individually to the lowest effective level according to tolerability”*. However, these country labels include the word *“titrated”* implying a similar concept (adjustment to optimize treatment).

Rheumatoid arthritis is an approved indication in all EU countries. There are some deviations regarding recommended dose. In Cyprus and Greece, the current labels recommend a dose of 2.5 mg/kg/day instead of 3 mg/kg/day and the maximum dose of 4 mg/kg/day instead of 5 mg/kg/day. Furthermore, in the Netherlands, the initial dose is recommended to be 2.5 mg/kg/day instead of 3 mg/kg/day. For maintenance the recommended dose is 3-4 mg/kg/day. In Sweden, the initial dose is also 2.5 mg/kg/day (and not 3 mg/kg/day, as claimed by the MAH in the statement that the proposed referral SmPC is in accordance with the SmPC in Sweden). The MAH considers the studies performed and review in the submitted documentation which used doses that ranged from 2.5 to 5 mg/kg/day are in support of the proposed label. However, the MAH is asked to justify the initial dose of 3 mg/kg/day, since this is in fact an increase from the currently approved initial dose of 2.5 mg/kg/day in several MS, implying that 2.5 mg/kg/day would not be an efficacious initial dose. The MAH provided efficacy data from EU and the US studies; since the starting dose of 3.0 mg is already recommended in 20 EU countries, this dose is also for harmonisation purposes the recommended starting dose in RA.

- Psoriasis:

“Due to the variability of this condition, treatment must be individualised. For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5 mg/kg. Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 6 weeks on 5 mg/kg/day, or in whom the effective dose is not compatible with the established safety guidelines (see section 4.4).”

Initial doses of 5 mg/kg/day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Sandimmun Neoral may be discontinued and subsequent relapse managed with re-introduction of Sandimmun Neoral at the previous effective dose. In some patients, continuous maintenance therapy may be necessary.

For maintenance treatment, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg/day.”

Psoriasis is an approved indication in all EU countries and the posology section is fairly similar in the respective SmPCs. The MAH has made a reasonable suggestion for this section of the SmPC taking the nationally approved deviating SmPCs into account. In addition, the MAH submitted documentation in which comprehensive clinical data on psoriasis were reviewed, presenting data in adult patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate. However, in line with the proposal for atopic dermatitis (see below), the CHMP is of the view that the following statement should be added, since ciclosporin is a potent substance, which requires a certain experience by the prescribing physician:

“Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of psoriasis.”

- Atopic dermatitis:

“Due to the variability of this condition, treatment must be individualized. The recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses. If a starting dose of 2.5 mg/kg/day does not achieve a satisfactory response within two weeks of therapy, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg/day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, Neoral should be discontinued. Subsequent relapse may be managed with a further course of Neoral.

Although a course of 8 weeks' therapy may be sufficient to achieve clearing, up to 1 year's therapy has been shown to be effective and well tolerated, provided the monitoring guidelines are followed.”

The MAH is proposing a dosage and administration wording as approved in 21 EU national labels.

Atopic dermatitis is an approved indication in all EU countries and the posology section including the recommended duration of treatment is fairly similar in the respective SmPCs. The MAH has made a reasonable suggestion for this section of the SmPC taking the nationally approved deviating SmPCs into account. In addition, the MAH submitted documentation in which comprehensive clinical data on atopic dermatitis were reviewed, presenting data in adult patients with severe atopic dermatitis in whom systemic therapy is required. However, in line with the proposal for psoriasis and in line with the SmPCs for topical calcineurin inhibitors used in this indication, the following statement should be added, since ciclosporin is a potent substance, which requires a certain experience by the prescribing physician:

“Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.”

Switching from Sandimmun to Sandimmun Neoral

The MAH proposed a wording for recommendations related to the switch between Sandimmun and Sandimmun Neoral in accordance with the approved wording of 9 countries. Not all countries have such a text included in their national labels and in some countries only Sandimmun Neoral is available.

In countries with a deviating wording, the overall recommendations are generally the same as in the text proposed by the MAH, but there is different order of presentation of the information. Some countries have very extensive texts.

The French label states that systematic switching should not be conducted or should only be conducted in patients with absorption problems. However, Sandimmun is not available in all countries and since the pharmacokinetic variability is lower with Sandimmun Neoral it does not appear adequate to advice against a switch.

Some countries have information about adverse events that may occur post-switching, however, it is agreed with the MAH that this should not appear in section 4.2.

Some countries have recommendations to monitor the safety clinical parameters during the first 3 months and not 2 months as proposed in the harmonized label. The MAH considers that this difference is not clinically relevant as patients on ciclosporin are monitored for even longer periods of time. This view is shared by the CHMP

Since not all countries have such a text included in their national labels and in some countries only Sandimmun Neoral is available, the MAH recommended to shorten the proposed text. The CHMP is in agreement with this approach. The following wording was agreed:

“The available data indicate that after a 1:1 switch from Sandimmun to Sandimmun Neoral, the trough concentrations of ciclosporin in whole blood are comparable. In many patients, however, higher peak concentrations (C_{max}) and increased exposure to the active substance (AUC) may occur. In a small percentage of patients these changes are more marked and may be of clinical significance. In addition, the absorption of ciclosporin from Sandimmun Neoral is less variable and the correlation between ciclosporin trough concentrations and exposure (in terms of AUC) is stronger than with Sandimmun.

Since the switch from Sandimmun to Sandimmun Neoral may result in increased exposure to ciclosporin, the following rules must be observed:

In transplant patients, Sandimmun Neoral should be started at the same daily dose as was previously used with Sandimmun. ciclosporin trough concentrations in whole blood should be monitored initially within 4 to 7 days after the switch to Sandimmun Neoral. In addition, clinical safety parameters such as renal function and blood pressure must be monitored during the first 2 months after the switch. If the ciclosporin trough blood levels are beyond the therapeutic range, and/or worsening of the clinical safety parameters occurs, the dosage must be adjusted accordingly.

In patients treated for non-transplantation indications, Sandimmun Neoral should be started with the same daily dose as was used with Sandimmun. Two, 4 and 8 weeks after the switch, renal function and blood pressure should be monitored. If blood pressure significantly exceed the pre-switch levels or if eGFR decreases by more than 25% below the value measured prior to Sandimmun therapy at more than one measurement, the dose should be reduced (see also ‘Additional precautions’ in section 4.4). In the event of unexpected toxicity or inefficacy of ciclosporin, blood trough levels should also be monitored.”

Switching between oral ciclosporin formulations

The wording proposed by the MAH is already approved in 24 countries and several other countries have very similar information. Three countries have no information in the national label explaining the conversion between oral ciclosporin formulations. The MAH considers that the information included in the proposed harmonized label provides relevant information to the prescribing physician to optimize patient management. However in view of the CHMP concerns the MAH revised and shortened the initially proposed text.

The CHMP requested subsequently to delete the words “with caution” due to the fact that there is no reason to assume that ciclosporin levels will be different to a relevant degree upon changing to a generic ciclosporin formulation. For generic ciclosporin formulations, bioequivalence has been demonstrated according to detailed and strict requirements. With this proof of bioequivalence, generic exchange is considered possible without restriction. The MAH accepted the deletion of “with caution” and considered that inclusion of more explicit advice should be provided to physician. The following wording was agreed:

Switching between oral ciclosporin formulations

The switch from one oral ciclosporin formulation to another should be made under physician supervision. Blood levels of ciclosporin should be monitored at time of the switch between modified vs. non-modified formulations or between different types of modified formulations to ensure that pre-switch levels are attained.

Special populations

- Patients with renal impairment

The MAH proposed the following wording for the above-mentioned paragraph:

All indications

Ciclosporin undergoes minimal renal elimination and its pharmacokinetics are not affected by renal impairment (see section 5.2). However, due to its nephrotoxic potential (see section 4.8), careful monitoring of renal function is recommended (see section 4.4).

Non-transplantation indications

With the exception of patients being treated for nephrotic syndrome, patients with impaired renal function should not receive ciclosporin (see subsection on additional precautions in non-transplantation indications in section 4.4). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day."

The proposed wording is not available in any of the countries. However, the MAH considered that this information was relevant to the prescribing physician to optimize patient treatment and improve outcomes.

The CHMP agreed with the MAH that the paragraph on patients with renal impairment should be included in section 4.2. However concerning pharmacokinetics, the word "extensively" should be added since the clearance of ciclosporin is actually lower in subject with renal impairment, leading to the following agreed wording:

"Ciclosporin undergoes minimal renal elimination and its pharmacokinetics are not extensively affected by renal impairment (see section 5.2)."

- Patients with hepatic impairment

The MAH proposed the following wording for the above-mentioned paragraph:

"Ciclosporin is extensively metabolised by the liver. The terminal half-life varied between 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease (see section 5.2). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see sections 4.4 and 5.2)"

The proposed text regarding dosage and administration in patients with hepatic dysfunction is not included in the label of any of the European Member States. However, the MAH considered that the information provided in the proposed text was relevant to the prescribing physician to improve patient outcomes.

The CHMP agrees with the MAH's proposal to include a paragraph on "patients with hepatic impairment" in section 4.2. The MAH agreed to add that ciclosporin blood levels should be monitored until stable concentrations are achieved since the time to achieve steady state will be somewhat longer in hepatically impaired subjects. The following wording was therefore agreed:

"Ciclosporin is extensively metabolised by the liver. An approximate 2- to 3-fold increase in ciclosporin exposure may be observed in patients with hepatic impairment. Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see sections 4.4 and 5.2) and it is recommended that ciclosporin blood levels are monitored until stable levels are reached."

- Paediatric population

The MAH proposed the following wording for the above-mentioned paragraph:

“Clinical studies have included children from 1 year of age using standard ciclosporin dosage of the oral formulations with no particular problems. In several studies, paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults.

Use of Sandimmun Neoral in children for non-transplantation indications other than nephrotic syndrome cannot be recommended (see section 4.4).”

None of the countries have a text that is completely aligned to the proposed harmonized text. The MAH had summarized pediatric data from patients with nephrotic syndrome and referred to these as a basis for the proposed SmPC text.

The CHMP is partially in agreement with the proposed following. The following wording (*paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults and Use of Sandimmun Neoral in children for non-transplantation indications other than nephrotic syndrome cannot be recommended*) is endorsed. However the CHMP requested the MAH to delete the wording proposed in the first sentence (i.e. use of the wording “*standard ciclosporin dosage*” and “*with no particular problems*”). The MAH revised the wording accordingly. The following wording was agreed:

“Clinical studies have included children from 1 year of age. In several studies, paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults.

Use of Sandimmun Neoral in children for non-transplantation indications other than nephrotic syndrome cannot be recommended (see section 4.4).”

- Elderly population

The proposed wording proposed by the MAH was the one approved in 20 EU Member States. Several countries do not have that detailed information or somewhat different wording. The CHMP proposed amendments (deletions, additions); the MAH implemented those accordingly, leading to the following agreed wording:

~~*“Experience with Neoral in the elderly is limited, but no particular problems have been reported following use at the recommended dose.*~~

~~*In rheumatoid arthritis clinical trials with ciclosporin, 47.5% of patients were aged 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises $\geq 50\%$ above the baseline after 3 to 4 months of therapy.*~~

~~*Clinical studies of ciclosporin in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, a*~~
~~*Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or medication and increased susceptibility for infections.”*~~

Method of administration

The MAH proposed the following wording for the above-mentioned paragraph:

Oral use

Sandimmun Neoral capsules should be swallowed whole.

Sandimmun Neoral oral solution should be diluted, preferably with orange or apple juice. However, other drinks, such as soft drinks, can be used accordingly to individual taste. The solution should be stirred well immediately before it is taken. Owing to its possible interference with the cytochrome P450-dependent enzyme system, grapefruit or grapefruit juice should be avoided for dilution (see section 4.5). The syringe should not come in contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue (see section 6.6).

The wording related to the method of oral administration as mentioned above is approved in 12 EU countries.

The proposed wording is acceptable to the CHMP.

Sections 4.3 to 4.9 – from “Contraindications” to “Overdose”

The approach taken by the MAH to achieve a proposed harmonized SmPC with regard to the safety sections of the SmPC (sections 4.3 to 4.9) was to use as a basis:

- The most recently updated Novartis CDS of Sandimmun Neoral, dated 13 February 2012 as justified by a review of submitted legacy studies, and identified literature references.
- The finalized Core Safety profile (CSP), from the last PSUR 13 work sharing procedure (EE/H/PSUR/0007/001).

According to the EU guideline on the implementation of the outcome of a PSUR WS procedure, the 29 EU countries have submitted, within a 4 month-timeframe after the release of the CSP, a variation to implement the agreed CSP.

Given the fact that a harmonized label was agreed among the EU community in February 2011 through the PSUR 13 WS procedure, the MAH position was to use the agreed core safety profile entirely (i.e. without any further changes). In November 2011, a full review of the company label (CDSs for both products Sandimmun and Sandimmun Neoral) was initiated. As an outcome of this full review, both CDSs were finalized with a release date of 13 February 2012. In that context, a thorough comparison of the Feb 2011 agreed CSP information and the safety sections of the newly released CDSs was performed.

To ensure that the Core Safety Information of the updated CDSs remains in line with the agreed CSP information, newly incorporated safety information into the CDS was proposed by the MAH for consideration into the agreed CSP, hence for the harmonized Eu SmPC safety related sections. Thus, the harmonized label for the safety section of the SmPC proposed by the MAH was based on the agreed CSP and enhanced with some newly added information from the full review of the MAH's labels (CDSs).

The CHMP is in agreement with the approach taken by the MAH i.e. to use the finalized Core Safety profile (CSP), from the last PSUR 13 work sharing procedure (EE/H/PSUR/0007/001), finalised in February 2011 as the basis for these SmPC sections. In addition, following a recent update of the Novartis CDS of Sandimmun Neoral, dated 13 February 2012, some revisions are proposed in comparison with the agreed CSP. Justifications have been provided for these deviations by the MAH.

Even if a CSP is available for Sandimmun, the CHMP has identified some issues warranting further revisions of the safety sections of the SmPC as outlined below in different sections.

Sections 4.3 – Contraindications

The MAH proposed the following wording for the above-mentioned paragraph:

“Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.”

As stated above, the MAH has used the CDS and the CSP to achieve a harmonized SmPC.

Ciclosporin is contraindicated for some HMG-CoA reductase inhibitors (statins) due to the CYP3A4 and/or Pgp inhibitory potential of ciclosporin. The MAH discussed the need of a contraindication of statins for cyclosporin and the need of further contraindications for other medicinal products/herbals.

For instance the CHMP considers that the use of Hypericum perforatum (St. John's wort, SJW) products in the treatment of a mild depression is not considered to balance the potential risk of an acute organ rejection caused by SJW induction; the CHMP requested the introduction of a contraindication accordingly. However concerning HMG CoA reductase inhibitors (statins), the CHMP agreed that a strict contraindication may not be warranted, however, information in section 4.4 should be strengthened.

In addition, the CHMP considered that substrates for CYP3A4 and/or P-gp and for which elevated plasma levels are associated with serious safety concerns should not be combined with ciclosporin (e.g. dabigatran, etexilate, bosentan, aliskiren). The MAH was asked by the CHMP to complement the list proposed in the SmPC, e.g. by taking into account the inhibitory effects of Ciclosporin on CYP3A4 in comparison with other, potent CYP3A4 inhibitors.

The MAH agreed to include the above mentioned contraindication, leading to the following agreed wording:

“Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination with products containing Hypericum perforatum (St John’s Wort) (see section 4.5).

Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren (see section 4.5).”

Section 4.4 - Special Warnings and Precautions for Use

Similar to section 4.2, this section includes sub-sections for different (non-transplantation) indications.

- *Medical supervision, Lymphomas and other malignancies, Geriatrics, Hyperkalaemia, Hypomagnesaemia and Hyperuricaemia, Special excipients:*

For the above mentioned sub-sections, the MAH proposed the CSP wording as the harmonised SmPC text. The CHMP therefore agreed with the wording proposed by the MAH.

- *Infections:*

The MAH proposed the CSP wording as the harmonised SmPC text and there is no difference compared with the CDS. The CHMP agrees with the wording proposed by the MAH. However, the CHMP considers that the name “John Cunningham” is not relevant to include in the SmPC and should be deleted. The MAH made this change accordingly.

- *Renal toxicity and hepatotoxicity:*

The MAH proposed to align the harmonized SmPC according to the agreed CSP. However, the word “occasionally” (that appears in the CSP, related to “reversible increases in serum bilirubin and, occasionally, in liver enzymes”) was removed to match the updated ADR section. Liver enzyme changes are to be considered as part of ADRs post-marketing on hepatotoxicity hence a frequency associated to this event is not definable.

Omission of the word “occasionally” is accepted by the CHMP. However, concerning the frequencies of ADRs based on post-marketing data, it is not agreed that the renal effects are reversible, since this is only true in the beginning of the treatment. The following changes are therefore proposed in the first part of this paragraph:

*A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during ~~the first few weeks of~~ Sandimmun Neoral therapy. These functional changes are dose-dependent and **are initially** reversible, usually responding to dose reduction.*

The following wording was agreed:

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during Sandimmun Neoral therapy. These functional changes are dose-dependent and are initially reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g. interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Frequent monitoring of renal function is therefore required according to local guidelines for the indication in question (see sections 4.2 and 4.8).

- *Monitoring ciclosporin levels in transplant patients:*

The MAH proposed the following wording for the above-mentioned sub-section:

“When Sandimmun Neoral is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure. For monitoring ciclosporin levels in whole blood, a specific monoclonal antibody (measurement of parent compound) is preferred; a high performance liquid chromatography (HPLC) method, which also measures the parent compound, can be used as well. If plasma or serum is

used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific monoclonal antibody and the non-specific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

It must be remembered that the ciclosporin concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters”.

The MAH proposed the above text which is in accordance with the CSP, with addition of the first sentence. When Sandimmun Neoral is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure.

The CHMP overall agrees with the wording proposed by the MAH, including the sentence added. However, in the sub-heading it is recommended to delete the words “in transplant patients” since monitoring of ciclosporin blood levels may not be used exclusively in transplant patients. The CHMP also recommended to include a sentence accordingly, leading to the following agreed wording:

“In non-transplant patients, occasional monitoring of ciclosporin blood levels is recommended, e.g. when Sandimmun Neoral is co-administered with substances that may interfere with the pharmacokinetics of ciclosporin, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).”

- *Hypertension:*

The MAH proposed the following wording for the above-mentioned sub-section:

“Regular monitoring of blood pressure is required during Sandimmun Neoral therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin, e.g. isradipine (see section 4.5).”

The MAH proposed the above text which is in accordance with the CSP, with addition of the last sentence “Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin, e.g. isradipine (see section 4.5). The CHMP agrees with the wording proposed by the MAH, including the sentence added.

- *Blood lipids increased*

The MAH proposed the following wording for the above-mentioned sub-section:

“Since Sandimmun Neoral has been reported to induce a reversible slight increase in blood lipids, it is advisable to perform lipid determinations before treatment and after the first month of therapy. In the event of increased lipids being found, restriction of dietary fat and, if appropriate, a dose reduction, should be considered.”

The MAH proposed the above text which is in accordance with the CSP, with omission of the words “on rare occasions” (the CSP states that “Since, **on rare occasions**, Sandimmun/ Sandimmun Neoral has been reported to induce...”). The MAH justifies the removal of this phrase was made to better reflect the given frequency of hyperlipidaemia in the ADR table, based on post-marketing data. The omission of the word “on rare occasions” is acceptable to the CHMP. However, concerning the frequencies of ADRs based on post-marketing data, there are comments related to the MAHs approach in section 4.8.

- *Live-attenuated vaccines*

The MAH proposed the following wording for the above-mentioned sub-section:

“During treatment with ciclosporin, vaccination may be less effective. The use of live attenuated vaccines should be avoided.”

The CSP wording is proposed by the MAH as the harmonized SmPC text. As the warning section is stronger than interaction, no proposal for inclusion of the proposed harmonized SmPC text on live-attenuated vaccines into the drug interactions section is warranted according to the MAH. The CHMP agrees with the wording proposed by the MAH.

- *Interactions:*

The MAH proposed the following wording for the above-mentioned sub-section:

“Caution should be observed while co-administering lercanidipine with ciclosporin (see section 4.5).

Ciclosporin may increase blood levels of concomitant medications that are substrates of P-glycoprotein (Pgp) such as aliskiren (see section 4.5). (...)”

The CSP wording is proposed by the MAH as the harmonized SmPC text. The CHMP does not entirely agree with the wording proposed by the MAH. Only a few examples of important interactions were given in the proposed text by the MAH. The CHMP suggested the following revision, to include all interactions of the same magnitude:

“Caution should be observed while co-administering ciclosporin with drugs or herbals that substantially increase or decrease ciclosporin plasma concentrations, through inhibition or induction of CYP3A4 and/or P-glycoprotein (see section 4.5).”

For the remaining sub-sections (namely *“Additional precautions in non-transplant indications, Endogenous uveitis, Nephrotic syndrome, Rheumatoid arthritis, atopic dermatitis and Paediatric use in non-transplant indications”*), the CSP wording was proposed by the MAH as the harmonized SmPC text, on which the CHMP proposed amendments which were subsequently endorsed by the MAH (cf. section 4.2).

Section 4.5 - Interaction with Other Medicinal Products and Other Forms of Interaction

The MAH proposed wordings for the sub-sections *Food interactions, Drug interactions, Drugs that decrease ciclosporin levels, Drugs that increase ciclosporin levels, Other relevant drug interactions, Recommendations, Paediatric population and Other relevant drug interactions.*

The MAH proposed the CSP wording as the harmonized SmPC text for all sections except the additional text regarding interactions with bosentan/ ambrisentan and anthracycline antibiotics.

The CHMP did not agree with the wording proposed by the MAH in this section. The CHMP provided the MAH with a detailed suggestion of a clearer structure and proposed text revisions accordingly. The CHMP also requested the MAH to provide more detailed information that could help the dose adjustments. Lastly the CHMP was of the view that further additions to the lists of interactants would be of value, based on an updated survey. Some suggestions were as follows: Aprepitant, bicalutamide, acetazolamide, chloramphenicol, quinupristin/dalfopristin, Phenobarbital, berberine, minoxidil, muromonab-CD3, cisapride (if licenced in any EU country), dronedarone, irinotecan, pemetrexed, docetaxel, paclitaxel, dabigatran, boceprevir, telaprevir, topotecan, trabectedin and lapatinib. Finally the MAH was also requested to update this section with more information concerning the inhibitory potential of ciclosporin on other transporters than P-gp.

The MAH provided the requested data and clarifications accordingly. An harmonised wording was therefore agreed.

Section 4.6 - Pregnancy and Lactation

The MAH proposed a wording on which the CHMP agreed with the exception of one minor comment, leading to the below agreed wording:

“Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits.

Experience with Sandimmun Neoral in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

A limited number of observations in children exposed to ciclosporin in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal. However, there are no adequate and well-controlled studies in pregnant women and therefore Sandimmun

Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The ethanol content of the Sandimmun Neoral formulations should also be taken into account in pregnant women (see section 4.4).

Breast-feeding

Ciclosporin passes into breast milk. The ethanol content of the Sandimmun Neoral formulations should also be taken into account in women who are breast-feeding (see section 4.4). Mothers receiving treatment with Sandimmun Neoral should not breast-feed because of the potential of Sandimmun Neoral to cause serious adverse drug reactions in breast-fed newborns/infants. A decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product to the mother.

Fertility

There is limited data on the effect of Sandimmun Neoral on human fertility (see section 5.3)."

Section 4.7 - Effects on Ability to Drive and Use Machines

The MAH proposed the following wording:

"No data exist on the effects of Sandimmun Neoral on the ability to drive and use machines."

The MAH proposed to harmonise the SmPC text along with the agreed CSP. The CHMP agreed with the wording proposed by the MAH.

Section 4.8 - Undesirable Effects

The MAH proposed wordings for the sub-sections *Summary of the safety profile, Doses/side effects, Infections and infestations and Neoplasms, Other ADRs from post-marketing experience.*

With regards to the sub-section *Summary of the safety profile*, the MAH proposed the inclusion of an overall summary of the principal adverse reactions which were most frequently reported in clinical trials, leading to the following statement:

"The principal adverse reactions observed in clinical trials and associated with the administration of ciclosporin include renal dysfunction, tremor, hirsutism, hypertension, diarrhoea, anorexia, nausea and vomiting."

The CHMP agrees with this addition as proposed by the MAH.

Regarding the sub-sections *Doses/side effects, Infections and infestations and Neoplasms, Other ADRs from post-marketing experience*, the MAH proposed align the harmonized SmPC text with the agreed CSP. The CHMP was in agreement with this approach and related wordings as proposed by the MAH.

Concerning the wording contained in the sub-section *Tabulated summary of ADRs*, the MAH has made a complete revision of the ADR table and changed many of the frequency figure, in most cases based on the fact that several ADRs originate from post-marketing data and a denominator was missing for the estimation of a frequency. In addition, the CHMP considers that the category "not known" should only be used in exceptional cases according to the SmPC guideline (September 2009). The recently issued CSP includes frequency categories for ADRs that have now been re-classified as "not known". This was not accepted by the CHMP and the MAH was requested to adhere to the classification according to the CSP unless adequately justified. More specifically, considering data on ADRs frequencies in clinical trials the CHMP requested the MAH to state the reasons to set different frequencies comparing to the ones that have been calculated and thus, proposals are:

- **Hyperglycaemia** ("very common" should be replaced by "**common**");
- **Headache** ("very common" should be replaced by "**common**");
- **Migraine** (not mentioned in SmPC but intended to be stated as "**unknown**");
- **Abdominal discomfort** ("very common" should be replaced by "**common**");
- **Gingival hyperplasia** ("very common" should be replaced by "**common**").

The MAH accepted the proposal to amend the ADRs as suggested. The main concern of CHMP was addressed and MAH updated the Section 4.8 according to data available and corrected majority

frequencies of ADRs requested. Other changes were introduced as well, including several proposed downgraded positions; justification were requested by the CHMP. In addition, the MAH clarified as requested why conjunctivitis, depression and hearing loss were not included in the ADR table.

A revised wording was proposed by the MAH accordingly and endorsed by the CHMP.

Finally in this section, the MAH also proposed two additions to this section, under the following wording for a new sub-sections on *Acute and chronic nephrotoxicity* and *Paediatric population*:

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitor (CNI) therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of acute or chronic nephrotoxicity. There have been reports from clinical trials and from the post-marketing setting associated with the use of Sandimmun Neoral. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see section 4.4).

Paediatric population

Clinical studies have included children from 1 year of age using standard ciclosporin dosage with a comparable safety profile to adults.

These paragraphs were not included in the CSP. The CHMP is of the view that the proposed text is relevant to include and therefore the CHMP agrees with the wordings proposed by the MAH.

Section 5.1 - Pharmacodynamic Properties

The MAH proposed an harmonized text based on the wording already approved in most EU countries. Only some minor differences were noted in the wording among the remaining countries in their nationally approved labels. The MAH proposed wording was in line with the overall strategy undertaken to propose a harmonized wording based on the most commonly approved label across the EU community. The CHMP therefore agrees with the approach taken by the MAH. However the CHMP considers that data of use in children in Nephrotic syndrome should be included under the heading *Paediatric population*. This point was addressed by the MAH and the following wording was added:

"Paediatric population: Ciclosporin has been shown to be efficacious in steroid-dependent nephrotic syndrome..."

In addition, the CHMP requested the MAH to provide a clear rationale for having slightly different description of pharmacodynamic section in Sandimmun (both oral and injection) vs Neoral versions of SmPCs. The main concern of CHMP was that slightly different description of pharmacodynamic section in Sandimmun (both oral and injection) vs Neoral. The MAH agreed to correct this and proposed a wording acceptable to the CHMP.

Section 5.2 - Pharmacokinetic Properties

The MAH proposed wordings for the sub-sections Absorption, Distribution, Biotransformation and Elimination, Special populations and Paediatric population.

The MAH' proposed harmonized text is already approved in 13 EU countries. Some differences were noted in the wording among the remaining countries in their nationally approved labels. The MAH proposed' wording was line with the overall strategy undertaken to propose a harmonized wording based on the most commonly approved label across the EU community.

The MAH has dedicated the whole sub-section to a comparison between Sandimmun and Sandimmun Neoral. This was supported since it is of interest in the states where both formulations are used. Furthermore, the CHMP requested the MAH to present the data in the wfollowing way: absolute figures for Tmax (with variability), absolute bioavailability and the effect of concomitant food intake) should be reported first, thereafter a short description of the difference between the formulations can follow. Finally , the CHMP requested clarifications in support to the wording proposed by the MAH.

The MAH addressed the points raised by the CHMP and proposed a final wording for this section on which the CHMP agrees.

Section 5.3 - Preclinical Safety Data

The MAH proposed a wording that was approved in between 18 and 24 MS, depending on sub-sections. Although the proposed text was already approved in the majority of EU countries, the CHMP is of the opinion that some structural modification of the text was needed. Furthermore, since ciclosporin from a non-clinical point of view is a well-known compound, the CHMP requested the MAH to delete the paragraph concerning clinical safety data on development of malignancy.

The MAH addressed the points raised by the CHMP and proposed a final wording for this section on which the CHMP agrees.

Section 6.3 - Shelf life

The CHMP requested the MAH to clarify the discrepancy in the shelf life term.

The CHMP was concerned by different shelf-life periods. The MAH explained that shelf life periods are not harmonised and proposed to follow the safest approach to Sandimmun (to fix 36 months period) and the last reduced period for Neoral that is approved in EU countries via variation procedure. The CHMP is in agreement with the MAH's approach.

Section 6.4 - Special precautions for storage

- Sandimmun 50 mg/ml concentrate for solution for infusion

The MAH proposed a correction in the wording of the *"Special precautions for storage"* in the SmPC for Sandimmun 50 mg/ml concentrate for solution for infusion, in order to align with the Guideline on Declaration of Storage Conditions (CPMP/QWP/609/96/Rev 2 dated 19 Nov 2007).

The MAH has inadvertently mentioned the Storage instructions of Sandimmun concentrate for solution for infusion as "Store below 25°C" in the harmonized SPC (under section 6.4: Special precautions for storage) submitted to the EMA in April 2012. The MAH confirms that the stability studies have been performed at the long term conditions at 25°C/60%RH and accelerated conditions also at 40°C/75% RH. The stability data at these testing conditions has shown that the results are within the acceptance criteria and the product is stable.

Therefore, The MAH adheres to the statement on SPC and PL as *"This medicinal product does not require any special temperature storage conditions"* in conformance to European Medicines Agency Guideline on Declaration of Storage Conditions (CPMP/QWP/609/96/Rev 2 dated 19 Nov 2007).

A new proposed wording was proposed by the MAH and agreed by the CHMP:

"Store below 25°C This medicinal product does not require any special temperature storage conditions. Store in the original package. Once an ampoule has been opened, the contents should be used immediately. Following dilution, the solution should be used immediately. If it is not used immediately, the conditions and duration of storage are the responsibility of the user and storage should not be longer than 24 hours at 2 to 8°C, unless dilution has been carried out under controlled and validated aseptic conditions."

- Sandimmun Neoral soft gelatin capsules

The MAH confirmed that the storage conditions in the SmPCs of the other pharmaceutical forms of ciclosporin are already aligned with the requirements set in the Guideline on Declaration of Storage Conditions (CPMP/QWP/609/96/Rev 2 dated 19 Nov 2007).

2.3. Recommendation

In conclusion, based on the assessment of the MAH's proposal, the responses to the LoQ, LoOI and following the discussions of the committee, the CHMP agreed upon and adopted harmonised sets of PI documents for the various presentations of Sandimmun Neoral and associated names.

Based on the above the CHMP considers the benefit/risk ratio of Sandimmun Neoral to be favourable and the harmonised PI to be approvable.

2.4. Conclusions

The basis for this referral procedure was the harmonisation of the SmPC, labelling and package leaflet. The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments from the marketing authorisation holder,

the CHMP was of the opinion that the benefit/risk ratio of Sandimmun Neoral and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Sandimmun Neoral and associated names (see Annex I of CHMP opinion).