Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Overall summary of the scientific evaluation of Sandimmun and associated names (see Annex I)

Sandimmun is an oil-based formulation of ciclosporin. Ciclosporin is a potent immunosuppressive agent 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. 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), Sandimmum 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 Sandimmum 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.

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, as amended. 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 as amended, to resolve divergences amongst the nationally authorised Sandimmun Neoral SmPCs across the EU/EEA region.

- **Clinical aspects**

To achieve a harmonized SmPC, the MAH used the wording that is common to national SmPCs in the majority of MSs and the MAH's Core Data Sheet (CDS) for Sandimmun Neoral (dated 13 February 2012), as well as submitted legacy studies and literature references. 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 also used.

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

Section 4.1 – Therapeutic indications

Transplantation indications

- *Solid organ transplantation:*

In line with the overall above mentioned strategy, the MAH proposed an indication wording which is already approved as proposed in 21 EU national labels.

The CHMP questioned the MAH's justification with regards to the listing of specific organ transplantations in the indication. The MAH agreed with the CHMP that no specific organ transplantations should be mentioned in section 4.1 unless not appropriate to use. The wording was reviewed accordingly.
With regards to the treatment of rejection, the main concerns reflected by the CHMP related to the switch from tacrolimus, treatment of humoral rejections with Cyclosporin and in case of chronic allograft injury, as this has been seen as chronic rejection. 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. The MAH addressed this concern; based on the submitted data the CHMP agreed with the MAH that the common practice is to change to another agent in case of rejection. Finally the inclusion of the term *"cellular"* rejection was also discussed since the diagnosis of humoral rejection episodes is controversial. The CHMP is of the view that introducing Sandimmun for the treatment of rejection is most appropriate for cellular rather than humoral rejection, based on the mechanism of action of CNI's. The MAH agrees with the CHMP's view. The proposed wording was reviewed and agreed accordingly.

- *Bone marrow transplantation (BMT)*

All MS except Norway have the indication bone marrow transplantation and GVHD approved.

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. 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 beyond the benefits/risk (B/R) of conditioning treatment. In their response the MAH confirmed that 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. In addition, a clarification of the B/R of ciclosporin in prevention of graft rejection after non-myloablative stem cell transplantation was also requested by the CHMP; the CHMP reviewed the MAH's position and considered unnecessary to specify myeloablative vs. non-myeloablative stem cell transplantation in the Ciclosporin indication.

Finally the CHMP also requested the MAH to discuss whether the heading "*bone marrow transplantation"* shall be updated to "*allogenous stem cell transplantation"*, i.e. independent from the source (else than non-host) of the stem cells and blasts. The MAH addressed the CHMP's concerns; the CHMP is of the view that clinical experience supports the proposed additions in the indication. A wording was agreed accordingly.

- Sandimmum and associated names 50mg/ml concentrate for solution for infusion

The CHMP noted that Marketing Authorisations for Sandimmum and associated names 50mg/ml concentrate for solution for infusion are solely granted for the above-mentioned transplantation indications (namely, the solid organ transplantation and the bone marrow transplantation). This was confirmed within the framework of this article 30 procedure.

Non-transplantation indications

- *Endogenous uveitis*

The MAH's proposed indication wording for the uveitis and Behçet uveitis is approved in 14 EU countries.

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 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.
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.

The CHMP also raised questions regarding the risk of aggravation of the neurological manifestations of Behcet's disease by Ciclosporin. 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 Behcet's disease in patients without neurological manifestations. A wording was agreed accordingly.

- *Nephrotic syndrome (NS)*

The MAH's proposed indication wording for nephritic syndrome is approved in 16 EU countries.

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). In parallel of these 9 performed studies, 2 double-blind placebo controlled multicenter studies and 1 multicenter study comparing ciclosporin with cyclophosphamide in steroidresistant patients had to be stopped prematurely because of a lack of suitable patients consenting to receive placebo or a cytostatic agent.

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 considered 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 in different forms of nephrotic syndrome in children and adults.

However the CHMP had concerns over the fact that current indication was 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 MAH agreed with the CHMP's opinion and a wording was agreed accordingly.

- *Rheumatoid arthritis (RA)*

The MAH's proposed indication wording for rheumatoid arthritis is approved in 13 EU countries.

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."*

- *Psoriasis*

The Psoriasis is an approved therapeutic indication in all EU countries. 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 wording proposed by the MAH.

- *Atopic dermatitis*

The MAH proposed the following wording for this indication: *"Sandimmun is indicated in patients with severe atopic dermatitis when systemic therapy is required."* The MAH's proposed indication wording for the Atopic dermatis is approved in 15 EU countries.

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 only approved in France. As recorded in the minutes of the pre-referral meeting held on 27 July 2011, 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 Members States, the Sandimmun and Sandimmun 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 Sandimmum 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. However the statement "*The daily doses of Sandimmum should always be given in two divided doses"* was 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 formulation. 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, standardised 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 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 be administered on a consistent schedule with regard to time of day and relation to meals. "* This wording was endorsed by the CHMP.
Lastly, based on the fact that ciclosporin is a potent active substance associated with serious safety concerns, the CHMP was 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; a general wording was agreed and included accordingly in section 4.2.

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 wordings in sections 4.2 and 4.4.were agreed accordingly.

Transplantation indications:

The MAH proposed two different wordings for each of the paragraphs 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 Cmax 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. However, since the studies in the original Sandimmun dossier are old and the posology based on those data is therefore obsolete in comparison with the different transplantation regimens used today, the CHMP was of the view that the dosage should also be guided by monitoring of ciclosporin blood levels. The MAH agreed with the CHMP's opinion and hence revised the wording of the posology in the solid organ transplantation indication accordingly.

- *Bone marrow transplantation*

Extensive information was provided by the MAH, including the dosages used in clinical studies that supported the approval of Sandimmun and Sandimmun Neoral in the bone marrow transplant indications. After review of the dataset, the proposed posology in the bone marrow transplantation indication as approved in 16 EU MS was acceptable to the CHMP.

<u>Non-transplantation indications:</u>

The MAH proposed a new general wording to introduce the paragraph on non- transplantation indications, as general recommendations. The CHMP agreed that general information applicable to all these indications was relevant to include. However the CHMP considered 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, in addition to a strengthening of the monitoring of renal function, the CHMP was of the view that occasional monitoring of ciclosporin blood levels were also relevant in these indications. The MAH proposed a wording accordingly to include these recommendations, as requested by the CHMP.

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. However, in case of a more prolonged inability to use oral ciclosporin, use of IV ciclosporin should be considered, provided that care is taken to administer an adequate IV dose. Thus, a wording was proposed by the MAH and agreed by the CHMP to address this matter.

Further to this introduction paragraph on non-transplantation, the MAH proposed a posology for each of the non-transplantation indications (i.e. endogenous uveitis, nephrotic syndrome, rheumatoid arthritis, psoriasis, atopic dermatitis). 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 a harmonised wording of the section 4.2 accordingly for the non-transplantations indications.

<u>Switching from Sandimmun to Sandimmun Neoral</u>

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. 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 shortening the proposed text. The CHMP was in agreement with this approach and a revised wording was agreed consequently.

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. The MAH considered that the information included in the proposed harmonized label provided 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, leading for a final wording which was endorsed by the CHMP.

Special populations

Referring to the "non-transplantation indications" section, likewise, the MAH proposed a posology for each of the special populations (i.e. patients with renal impairment, patients with hepatic impairment, paediatric population, elderly population). 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 a harmonised wording of the section 4.2 accordingly for the special populations.

Method of administration

The MAH proposed the wording related to the method of oral administration which is approved in 12 EU countries. The proposed wording was 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 MAH's Core Data Sheet (CDS) of Sandimmun Neoral, dated 13 February 2012 (as justified by a review of submitted legacy studies, and identified literature references) and the finalized Core Safety profile (CSP) from the last PSUR 13 work sharing (WS) 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's position was to use the agreed CSP 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 by the MAH. 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 was in agreement with the approach taken by the MAH.

Sections 4.3 – Contraindications

As stated above, the MAH proposed a following wording for the above-mentioned paragraph based on the wordings used in the CDS and CSP.

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.

The CHMP considered that the use of Hypericum perforatum (St. John's wort, SJW) products in the treatment of a mild depression was 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 agreed to include the above mentioned contraindication. A wording was agreed accordingly.

Section 4.4 - Special Warnings and Precautions for Use

With regards to the paragraphs concerning *Medical supervision, Lymphomas and other malignancies, Geriatrics, Hyperkalaemia, Hypomagnesemia and Hyperuricaemia, Special excipients,* the MAH proposed the CSP wording as the harmonised SmPC text. The CHMP agreed with the wording proposed by the MAH.

Concerning the sub-sections on *infections, renal toxicity and hepatotoxicity, monitoring ciclosporin levels in transplant patients, hypertension, blood lipids increased, live-attenuated vaccines and interactions,* wordings were proposed by the MAH and intensively discussed and revisited as per CHMP requests.

Similarly to the section 4.2, wordings for each of the sub-sections for the different non-transplantation indications were discussed and agreed between the CHMP and MAH.

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. 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. A 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, which was taken into consideration subsequently by the MAH. A wording was agreed accordingly.

Section 4.7 - Effects on 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. The CHMP agreed with the addition 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 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 originated from post-marketing data and a denominator was missing for the estimation of a frequency. Whilst reviewing the MAH's proposal, in view of the SmPC guideline, the CHMP considered that the category "*not known*" should only be used in exceptional cases; 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 were made with regards to some ADRs such as *hyperglycaemia, headache, migraine, abdominal discomfort and gingival hyperplasia*. The MAH accepted the proposal to amend the ADRs as highlighted by the CHMP.

Other changes were also introduced including several proposed downgraded positions; justifications were requested by the CHMP and provided by the MAH subsequently. 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 proposed two additions to this section, under the format of two new sub-sections on *Acute and chronic nephrotoxicity* and *Paediatric population*. These paragraphs were not included in the CSP. The CHMP was of the view that the proposed text is relevant to include and therefore the CHMP agreed with the wordings as proposed by the MAH.

Section 5.1 - Pharmacodynamic Properties

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 agreed 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 a wording was agreed.

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 Sandimmun Neoral versions of SmPCs. The MAH agreed to correct this and proposed a wording for Sandimmum and Sandimmum Neoral which was 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." based on a harmonized text already approved in 13 EU countries. 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. This was endorsed by the CHMP with the exceptions of some requests for clarifications, which were subsequently provided by the MAH with supportive data.

The MAH 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.

Section 5.3 - Preclinical Safety Data

The MAH proposed a wording that was approved in between 18 an 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 agreed.

Section 6.3 - Shelf life

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

Section 6.4 - Special precautions for storage

The MAH confirmed that the storage conditions in the SmPCs of Sandimmun soft gelatin capsules and oral solutions 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).

In addition, 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, also in conformance to the above-mentioned Guideline. The MAH confirmed 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 adhered to the statement on SPC and PL as *"This medicinal product does not require any special temperature storage conditions"* in accordance with the guideline.
A new wording was proposed by the MAH and agreed by the CHMP.

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 and associated names.

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

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holder(s) have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Sandimmum and associated names (see Annex I).