

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**SANDIMMUN / SANDIMMUN NEORAL
(Ciclosporin)**

[25 mg, 50 mg, 100 mg soft gelatin capsules
100 mg/mL oral solution
50 mg/mL concentrate for solution for infusion for
Sandimmun

10 mg, 25 mg, 50 mg, 100 mg soft gelatine capsules
100 mg/mL oral solution for Sandimmun Neoral]

CZ/W/04/pdWS/01

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| Rapporteur: | The Czech Republic |
| Start of the procedure (day 0): | 15.02.2010 |
| Date of this report: | 26.04.2010 |
| Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70): | 26.04.2010 |
| Deadline for CMS's comments (day 85): | 11.05.2010 |
| Finalisation procedure (day 90): | 16.05.2010 |

ADMINISTRATIVE INFORMATION

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| Invented name of the medicinal product(s): | Sandimmun/Sandimmun Neoral See section VII |
| INN (or common name) of the active substance(s): | Ciclosporin |
| MAH (s): | Novartis See section VII |
| Pharmaco-therapeutic group (ATC Code): | Immunosuppressive agents L04A D01 |
| Pharmaceutical form(s) and strength(s): | 25 mg, 50 mg, 100 mg soft gelatin capsules 100 mg/mL oral solution 50 mg/mL concentrate for solution for infusion for Sandimmun 10 mg, 25 mg, 50 mg, 100 mg soft gelatine capsules 100 mg/mL oral solution for Sandimmun Neoral |
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INDEX

I. EXECUTIVE SUMMARY

II. RECOMMENDATION

III. INTRODUCTION

IV. SCIENTIFIC DISCUSSION

IV.1. Information on the pharmaceutical formulation used in the clinical studies

IV.2. Non-clinical aspects

IV.2.1 Introduction

IV.2.2 Non clinical studies

IV.2.3 Discussion on non clinical aspects

IV.3. Clinical aspects

IV.3.1 Introduction

IV.3.2 Clinical studies

IV.3.3 Discussion on clinical aspects

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

V.1. Overall conclusion

V.2. Recommendation

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

The results of the non-clinical studies and the 14 paediatric clinical studies presented by the company support the positive benefit-risk profile of Sandimmun and Sandimmun Neoral in the approved indications and are well in line with the current information in the company Core Data Sheet. Based on the review of the available documentation, no amendment to the existing CDS is warranted.

III. INTRODUCTION

Novartis Pharma A.G. has submitted all data available on the paediatric studies in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use on 30 October 2009. There are 14 clinical studies of paediatric relevance not yet submitted to the EU competent authorities concerning the active substance ciclosporin.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Sandimmun and Sandimmun Neoral and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- Cover letter
- EMEA/CMD request letter
- A short critical expert overview clarifying the context of the data and relevance for the EU situation

- Clinical expert CV and signature
- Relevant non-clinical studies and literature references
- Relevant clinical studies and literature references

CsA is a cyclic polypeptide consisting of 11 amino acids. CsA locks 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. Successful solid organ transplantation and bone marrow transplantation have been performed in man, using CsA to prevent and treat rejection and GVHD (graft versus host disease). Beneficial effects of CsA therapy have also been shown in a variety of conditions that are known, or may be considered, to be of autoimmune origin.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

There are oral solution, soft gelatine capsules and concentrate for solution for infusion used in clinical studies.

Sandimmun Neoral is microemulsified formulation of CsA and provides improved dose linearity in CsA exposure, a more consistent absorption profile and less influence from concomitant food intake and from diurnal rhythm compare to Sandimmun.

IV.2 Non-clinical aspects

1. Introduction

The MAH submitted 6 non-clinical study reports and 9 literature references to non-clinical aspects.

2. Non clinical studies

203-027 Fertility and general reproductive performance study in male and female rats (oral administration)

➤ Description

In this study, the effects of CsA (OL 27-400) on the reproductive performance was examined in male and female rats (Han Wistar). Animals of the F0 generation were treated orally with doses of 0, 1.5, 5, or 15 mg/kg/day, starting 9 weeks (males) or 2 weeks (females) prior to pairing and lasting until autopsy. F0 females were either killed and examined together with their foetuses shortly before term, or allowed to litter and rear their F1 offspring and then killed at weaning. F0 males were killed when most of the females had given birth. Normal physical, functional and behavioural development as well as fertility were assessed in F1 offspring.

Prolonged treatment with 5 or 15 mg/kg/day produced distinct in-life and post-mortem effects in F0 males as well as reduced weight gain, whereas no effects were observed at the 1.5 mg/kg/day dose level. Females were not affected up to the high dose. However, two dams showed dystocia and had to be killed. The reproductive performance of F0 animals was normal except for an increased perinatal mortality and questionable impaired postnatal development of F1 pups in single litters at the 15 mg/kg/day dose level. No adverse effects were noted at the lower doses. Fertility of randomly selected F1 animals and the development of their offspring were normal.

➤ **Results**

In view of the fact that adverse effects on reproduction occurred only at the highest dose level, which was well above the no-toxic-effect-level of adult animals, findings in this study cannot be regarded as prohibitive for the therapeutical use of OL27-400 in man.

203-010 A teratological study in rats

➤ **Description**

Inseminated rats were treated orally (by gavage) with CsA (OL 27-400) at dose levels of 10, 17, 30, 100 and 300 mg/kg, respectively, from day 6 to 15 post coitum (p.c.). The animals were killed on day 21 p.c. and examined together with their offspring. Maternal and fetal parameters were recorded and evaluated statistically.

At doses of 10 and 17 mg/kg/day, OL 27-400 was well tolerated by the dams, while at higher dose levels a dose-dependent increase of toxic effects was seen, including clinical signs, impaired weight development and mortality.

No relevant changes in reproductive parameters were seen at the 10 or 17 mg/kg/day dose levels, while from 30 mg/kg/day upwards, embryotoxic and fetotoxic effects occurred, resulting in an elevated embryonic mortality, reduced fetal weight and a higher incidence of skeletal retardations. A teratogenic activity, however, was not observed at any dose level where viable fetuses were obtained.

➤ **Results**

Since all the changes on reproductive parameters occurred at dose levels toxic to the dams, they are regarded as unspecific effects, and are, therefore, not considered to be prohibitive for the use of the compound in man.

203-007 A teratological study in rabbits

➤ **Description**

Inseminated rabbits were treated orally (by gavage) with CsA (OL 27-400) at dose levels of 10, 30, 100 and 300 mg/kg, respectively, from day 6 to 18 p.c. The rabbits were killed on day 29 p.c. and examined together with their fetuses. Maternal and fetal parameters were recorded and evaluated statistically.

OL 27-400 was well tolerated at the 10 and 30 mg/kg/day dose levels. 100 and 300 mg/kg/day proved to be increasingly toxic as the number of dams losing weight increased dosedependently.

In addition, about half of the females in these two groups showed enlarged mammary glands, which proved, however, to be normal lactating glands as the histopathological examination showed. The reproductive parameters were not impaired at the non-toxic dose levels. At the toxic dose levels of 100 or 300 mg/kg/day, the compound proved to be increasingly embryo- and fetotoxic, but not teratogenic.

➤ **Results**

In conclusion, in rabbits, OL 27-400 caused neither teratogenic nor embryo-lethal effects at doses up to 30 mg/kg/day.

203-023 Peri- and postnatal study in rats

➤ **Description**

A study was performed to investigate the effects of CsA (OL 27-400) on female rats and their offspring during the peri- and postnatal periods. Females were treated orally with doses of 5, 15, or 45 mg/kg/day, from day 15 p.c. until day 21 post partum (p.p.). The physical, functional and behavioural development as well as the fertility were assessed in the F1 offspring.

At the 45 mg/kg/day dose level the compound was clearly toxic for females and their offspring. This was shown by the reduced weight gain of the females during the last third of gestation and the increased pre-

and postnatal mortality rates of the offspring. No adverse effects were observed in the two lower dose groups.

➤ **Results**

In view of the toxicity of the 45 mg/kg/day dose to the dams, the findings observed in the offspring are considered to be of no consequence for the therapeutic use of OL 27-400 in man.

In the tolerated dose range up to 15 mg/kg, there was no evidence of any adverse effects.

203-038 General toxicity and reproductive performance study in pre- and postpubertal rats

➤ **Description**

A study on general toxicity and reproductive performance in pre- and postpubertal rats was performed. Male and female rats were orally treated with CsA (OL 27-400) starting at the age of 15 day and ending at the age of 70 or 74 days. Doses were 3, 6 or 9 mg/kg/day.

Animals of part 1 were killed at the end of the treatment period in order to make a detailed assessment of the general tolerance. Animals of part 2 were allowed to reach maturity and the reproductive performance and development of their offspring were assessed.

OL 27-400 was absorbed and eliminated by juvenile rats in a similar manner as in adult rats.

Plasma levels in males were about twice as high as those in females. There were no drug-related mortalities. Histological findings in the kidneys and the livers were minimal and gave no indication of a clear-cut drug effect. In both sexes body weights were reduced in a dose-dependent manner one week after the start of treatment. However, weights quickly returned to normal except in males at the high dose group indicating that the limit of tolerance was reached in these animals. This was further confirmed by the increased glucose and triglyceride levels. These adverse effects correlated well with the high plasma levels of OL 27-400 found in these animals.

➤ **Results**

Reproductive performance was unaffected, as was the development of the progeny of treated animals. In conclusion, OL 27-400 was well tolerated by juvenile animals up to 9 mg/kg/day, except for males which showed some signs of adverse effects, and had by far the highest plasma levels of the drug.

201-007 Transplacental passage in rats and rabbits

A study was performed to verify the absorption and the transplacental passage of ciclosporin (OL 27-400) in rabbits and rats. OL 27-400 was administered orally as a single dose to New Zealand rabbits at 30 mg/kg on day 17 p.c., and to Han Wistar rats at a dose of 15 mg/kg on day 15 p.c.

Peak plasma levels were obtained in rabbits at 4 hours after administration, and in rats at 2 hours after administration. Although rats received only half of the dose, compared to rabbits, peak plasma levels were 10 times higher than in rabbits. This may indicate a much better absorption of the compound in rats. Proof of transplacental passage of OL 27-400 was shown by the tissue levels in the embryonic compartments.

3. Discussion on non clinical aspects

Non-clinical studies relevant to paediatric indication of ciclosporin A have been presented clearly and comprehensively. There are not any discrepancies between study results and text of SPC and PIL for Sandimmun Neoral. Current SPC and PIL are considered adequate to the available information regarding administration of ciclosporin A to pediatric population. There are no changes in SPC or PIL needed. There are no comments on SPC and PIL texts with respect to the available non-clinical data.

IV.3 Clinical aspects

1. Introduction

The MAH submitted reports for:

OLN901 study: Pharmacokinetics of a new oral formulation of cyclosporine in pediatric liver transplant recipients

OLN106 study: Randomized, crossover, open-label study of the pharmacokinetics of the oral solution of Neoral in comparison to the oral solution of Sandimmun in stable pediatric liver transplant patients

OLN105 study: A randomized, crossover, open-label study of the pharmacokinetics of the oral solution of Neoral in comparison to the oral solution of Sandimmun in stable pediatric renal transplant patients

SF-09 study: Switching to Sandimmun Neoral, a new oral formulation of cyclosporin A, in children with a liver transplant

OLO ES02 study: Open-label pilot study on the efficacy and safety of Sandimmun Neoral for antirejection prophylaxis in pediatric primary orthotopic liver transplant patients

GB-03 study: Neoral in pediatric kidney transplant patients

The MAH submitted extended synopsis, publications for:

Neo B02 study: Clinical pharmacokinetics of Neoral in pediatric recipients of primary liver transplants

NEO I-05 study: Evaluation of Sandimmun Neoral pharmacokinetics in children awaiting renal transplant, correlation with post-transplant pharmacokinetics

SIM-Tx91/501 study: Evaluation of Sandimmun pharmacokinetics in pediatric patients awaiting renal transplant

GB-02 study: Neoral in pediatric heart transplant patients

OLN-US01 study: Cooperative clinical trials in pediatric transplantation, controlled trial of induction in renal transplantation

OLO9510 study: CsA (Sandimmun) in the treatment of nephrotic syndrome in adults and children with steroid resistant nephropathy with minimal histological lesions or focal and segmental glomerulosclerosis

OLO9511 study: CsA (Sandimmun) in the prevention of relapses of steroid-dependant nephrotic syndrome in adults and children

2. Clinical studies

Clinical pharmacology studies

OLN901 study: Pharmacokinetics of a new oral formulation of cyclosporine in pediatric liver transplant recipients

Pilot double-blind, single dose, crossover study comparing the absolute bioavailability of Cyclosporin (CsA) resulting from Sandimmun and Neoral oral solutions in de novo liver transplant recipients.

Pharmacokinetic (PK) profile at day 1 or 2 post-transplant was obtained 2 hours before, during and after the 2-hour intravenous (IV) infusion of CsA using 14 sequential blood sampling times (-2hr, 0hr, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hrs after beginning the infusion). Patients were randomized on the next day following the IV PK collection to receive a single dose of either Sandimmun or Neoral oral solution, (dose calculated as 3-times their IV infusion dose received on day 1). On the second day following the IV PK collection, patients received the alternate formulation of CsA at the same dose as the previous oral formulation. CsA concentrations were assessed using a monoclonal antibody radioimmunoassay specific for parent CsA (IncStar). PK parameters (AUC₀₋₁₂, C_{max}, C_o, T_{max}) were obtained by standard methods.

Totally 9 children completed this study. Mean age, weight and body surface area of patients were 2.5 years (range 6 months to 11 years), 14.3 ± 11.1 kg and 0.58 ± 0.33 m² respectively. Study was initiated at a mean date of 14 days post-transplant (range: 8 to 20 days). No adverse events (AEs) related to the study.

The mean absolute bioavailability for Neoral was significantly higher vs. Sandimmun (p=0.01). There were statistically significant correlations between age and mean absolute bioavailability for Neoral (r=0.87; p=0.02) in the 6 children aged 2 years or less.

➤ **Assessors comment:**

The absolute bioavailability was significantly higher in Neoral vs. Sandimmun oral formulation in children during liver post-transplant period.

OLN106 study: Randomized, crossover, open-label study of the pharmacokinetics of the oral solution of Neoral in comparison to the oral solution of Sandimmun in stable pediatric liver transplant patients

Randomized, multiple dose, crossover, open-label study to compare the bioavailability of CsA from the Neoral and Sandimmun oral formulations in stable pediatric liver transplant recipients. The secondary PK parameters as well as the clinical safety and tolerability well studied also.

Patients were stratified based on age in two groups: group 1 was 1 to 5 years and group 2 was 6 to 18 years. The study duration was of five weeks, with three successive treatment periods for each patient. Period I (days 1 through 14)- same dosage as that prior to study entry with the oral formulation of either Neoral or Sandimmun. Period II (days 15 through 28) - switched to Neoral or Sandimmun with same daily doses as in Period I. Period III (days 29 through 35) - all patients switched back to the formulation they received in Period I. CsA PK profiles done at days 14 and 28 in 12-hour scheme. CsA concentrations were

assessed using a fluorescence method (FPIA-TDx). PK parameters (AUC₀₋₁₂, C_{max}, C₀, T_{max}) were obtained by standard methods. AEs, vital signs, physical examinations and laboratory tests were determined and evaluated at each PK profiling period and at initiation and completion of the study.

Totally 31 patients entered and 27 completed the study; three discontinued due to AEs and one due to poor IV access which prevented adequate PK sampling. Median age according to groups 1 and 2 was 3.4 years and 10.8 years, respectively; mean weight according to groups 1 and 2 was 15.7 kg and 37.0 kg, respectively. M/F ratio according to groups 1 and 2 was 8/7 and 8/8, respectively. The bioavailability of CsA from Neoral was significantly greater than from the Sandimmun in both groups. All differences, except of T_{max} and C₀, between formulation PK values were statistically significant in both groups. Totally 3 patients discontinued the study due to AEs: severe acute rejection (possibly study drug related), gastroenteritis with electrolyte imbalance (not study drug related), and acute gastroenteritis (not study drug related). No deaths occurred during the study.

➤ **Assessors comment:**

The results of this study show that the safety and tolerability of the two formulations were similar in both groups of patients.

SF-09 study: Switching to Sandimmun Neoral, a new oral formulation of cyclosporin A, in children with a liver transplant

A Finnish open-label, single-center sequential switch study comparing the relative oral bioavailability of Neoral and Sandimmun and to examining the consequences of a formulation switch to Neoral in children with liver transplant.

Patients were stratified into 2 groups on the based of age, group I (age range 2 to 8 years; n=9) received formulation every 8 hours and group II (age range 8 to 15 years; n=8) received formulations every 12 hours. PK profiles were measured at days 1 and 5. CsA concentrations were assessed using a specific radioimmunoassay (Cyclo-Trac). PK parameters (AUC₀₋₁₂, C_{max}, C₀, T_{max}) were obtained by standard methods. Weight range for group I versus II were 12.6–23.0 kg vs. 20.8-104 kg. M/F ratios were 4/5 for group I and 4/4 for group II.

The bioavailability of CsA was significantly higher with Neoral in comparison to Sandimmun in both groups. The other PK parameters showed an improved and more rapid absorption of CsA from Neoral vs. Sandimmun in both groups. In group I, AUC and C_{max} were increased by 60% and 85% respectively for CsA from the Neoral formulation. A similar trend was note in group II with AUC and C_{max} increases of 74% and 96% respectively for Neoral vs Sandimmun. The differences were not as high, T_{max} values were consistently shorter for Neoral, reflecting a more rapid systemic absorption rate for CsA compared with the Sandimmun formulation. None of the subjects discontinued the PK analysis part of the study because of AEs.

➤ **Assessors comment:**

The stable pediatric liver transplant recipients of different age shown greater relative CsA exposure and faster rate of absorption in Neoral compared to Sandimmun oral formulation.

OLO ES02 study: Open-label pilot study on the efficacy and safety of Sandimmun Neoral for antirejection prophylaxis in pediatric primary orthotopic liver transplant patients

A Spanish open-label, phase IV, single-center, uncontrolled clinical trial to determine the CsA PK from the Neoral formulation in de novo pediatric liver transplant recipients. Initial dose was 15 mg/kg/day of Neoral oral solution by nasogastric tube day 1 post-transplant and continue until target levels were achieved (+/- Sandimmun IV). PK profiles were obtained 3 times daily at days 1, 2, 3 and 5 post-transplant. PK parameters (AUC, C_{max}, C₂, T_{max} and C₀) were calculated from each profiling day and correlated with incidence of acute rejection to determine the optimal monitoring. Totally 20 children were enrolled in this study and mean age was 3.2 years. The PK showed that the mean dose of CsA administered orally over the total duration of the study was 20.3 mg/kg/day. Fifty-five percent of children required intravenous CsA administration in the first day post transplant to achieve desired target C₀ levels. As mentioned, in study 9 children experienced acute rejection (45%) which was confirmed by biopsy. Eight of the nine rejections occurred in the first 2 weeks post-transplant (mean 8.4 days ± 8.4). One patient who experienced acute rejection required a switch from Neoral to tacrolimus. All children reported at least one AE, although 71% of AEs were not considered related to the immunosuppressive therapy by the investigator; 7.7% of AEs were considered serious.

➤ **Assessors comment:**

On the base of outcome the intravenous CsA administration was suggested in the first day of post tranplant period.

Neo B02 study: Clinical pharmacokinetics of Neoral in pediatric recipients of primary liver transplants

Open-label, uncontrolled, single-center study designed to determine the CsA PK from Neoral in pediatric liver transplant recipients to investigate the dosing and the absorption of CsA from the Neoral formulation.

Totally 10 new pediatric liver transplant recipients were enrolled in this study. Initially received IV CsA 2mg/kg every 24 hours until stable, and then switched to Neoral 5mg/kg every 12 hours. PK profiles were obtained at three time periods: PK-1 D1 IV CsA; PK-2 oral CsA profile after the first Neoral dose administration; PK-3 when steady-state on the Neoral regimen. CsA concentrations were assessed using a monoclonal immunoassay (mFPIA).

Median age of the 10 subjects was 1.15 years (range 0.8 to 2.5 years) and mean Neoral doses administered during the PK2 and PK3 profiling periods were 5.3 and 10.9 mg/kg per 12hours respectively. A strong correlation between C₀ and AUCs for both oral PK profiles (r = 0.93 for both PK2 and PK3 C₀ vs AUC correlations).

Adverse events: 2 children suffered from diarrhoea during the PK3 profiling only.

➤ **Assessors comment:**

No differences in mean PK data were identified; the episodes of diarrhoea did not impact the CsA absorption and exposure. Neoral had shown adequate absorption of CsA in children after liver transplantation.

OLN-US01 study: Cooperative clinical trials in pediatric transplantation, controlled trial of induction in renal transplantation

US randomized, multi-center, blinded study to evaluate the safety and efficacy of Neoral in pediatric renal transplant recipients over a 4-year period (Phase IV commitment to the FDA). Study design: patients were firstly randomized for either i.v. CyA or OKT3 treatment group and secondly to either Neoral or Sandimmun ones. Primary endpoint was to assess one year graft function; secondary endpoint was to determine efficacy and safety of Neoral at 2nd and 4th post-transplant year.

287 of 292 randomized patients received a kidney graft. 58% of children were below 12 years of age. 54% patients were transplanted from cadaver donor. 47% patients received concurrent MMF with the standard immunosuppressive regimen.

Kidney graft function at 1 year did not differ between CyA and OKT3 groups. One-year graft survival was 89.23% in the CyA group and 89.1% in the OKT3 group (p=0.19). Over a 4-year period 54% of patients experienced at least one rejection episode (166 in the CyA group, 172 in the OKT3 group), 19% of the grafts were lost in the CyA group, 27% in the OKT3 (p=0.154). 278 AEs were reported in the OKT3 and 276 in the CyA group. 52% vs 50% of at least one reported AE in the OKT3 vs CyA group. 8 children died in the OKT3 group, 4 in the CyA group. Graft survival was comparable between Neoral and Sandimmune (p=0.80). Graft function determined by eGFR (Schwartz formula) and serum creatinine was comparable between the Sandimmune and Neoral groups at year 1 post transplant (p=0.87) and the risk of rejection during the study period did not differ (p=0.22).

➤ **Assessors comment:**

The stability of CyA Neoral blood levels were superior to that in Sandimmune and reached statistical significance. There were no safety concerns regarding the Neoral in the pediatric kidney transplant population.

NEO I-05 study: Evaluation of Sandimmun Neoral pharmacokinetics in children awaiting renal transplant, correlation with post-transplant pharmacokinetics

Open-label, single-center, uncontrolled study in pediatric renal transplant candidates assessed CyA Neoral oral formulation PK profile. Study design was to determine the degree of CyA absorption and correlation with C0 and C2 sampling. The administered oral dose prior to renal transplantation was 7 mg/kg.

17 pediatric renal transplant candidates were enrolled to provide CyA Neoral PK profile. The mean age of the cohort was 10.3 ys, mean weight was 28.8 kg. M/F ratio was 7/10. All the patients with end-stage renal failure were either on hemodialysis or peritoneal dialysis.

Comparison with a historical control group with Sandimmun oral solution the Neoral CyA AUC0-12 better correlated with C2-C12. Cmax (1651 ng.mL) and Tmax (mean 1.7 hr) shown Neoral to be absorbed promptly and effectively. The C0 and AUC0-12 correlation was much improved after Neoral administration (r = 0.92) compared with the historical data from Sandimmun (r=0.16). Inter-subject variability in C0 levels of Neoral was lower than of Sandimmun following the same dose (30% vs 63%).

➤ **Assessors comment:**

The first Neoral dose in pediatric renal transplant candidates allows higher CyA exposure with reduced inter-subject variability of PK parameters when compared with historical controls of Sandimmun.

SIM-Tx91/501 study: Evaluation of Sandimmun pharmacokinetics in pediatric patients awaiting renal transplant

The open-label, single-center, uncontrolled study assessed pharmacokinetic parameters in pediatric renal transplant candidates. The study design was to get drug dosing information to avoid risk of early acute rejection and/or CyA toxicity in an early post-transplant period. The administered oral dose prior to renal transplantation was 7 mg/kg.

46 pediatric renal transplant candidates were enrolled to provide a single CyA Sandimmun PK profile. The mean age of the cohort was 12.8 ys, mean weight 36.8 kg. M/F ratio was 25/21. All the patients with end-stage renal failure were either on hemodialysis or peritoneal dialysis. The AUC slightly correlated with body weight (the highest correlation between blood levels and AUC was found at 4 hours ($r = 0.823$, $P < 0.001$)). The average AUC was 3147.1 h/g/ml. Four PK patterns were shown in the study: early or late peak, biphasic or flattened profile.

➤ **Assessors comment:**

Based on this study in 46 pediatric renal transplant patients, the optimal CyA dose should be determined prior to renal transplantation.

Clinical studies in transplantation

GB-02 study: Neoral in pediatric heart transplant patients

The UK, prospective, single-center, randomised, open-label, pilot study comparing the PK, efficacy and safety of Neoral and Sandimmun in de novo pediatric heart transplant recipients.

CsA was assigned around 24 hours after heart transplant. PK profile was performed at 12 hour regime around days 4 to 5 post-transplant and at day 14 or at discharge. CsA concentrations were assessed using a monoclonal immunoassay. Totally 6 children were enrolled in the study, M/F ratio was 1/5. But due to the difficulty in enrolling patients the study was prematurely discontinued.

➤ **Assessors comment:**

No analyses of the data were provided. The study was discontinued prematurely.

OLN-US01 study: Cooperative clinical trials in pediatric transplantation, controlled trial of induction in renal transplantation

US randomized, multi-center, blinded study to evaluate the safety and efficacy of Neoral in pediatric renal transplant recipients over a 4-year period (Phase IV commitment to the FDA). Study design: patients were firstly randomized for either i.v. CyA or OKT3 treatment group and secondly to either Neoral or

Sandimmun ones. Primary endpoint was to assess one year graft function; secondary endpoint was to determine efficacy and safety of Neoral at 2nd and 4th post-transplant year.

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➤ **Assessors comment:**

The stability of CyA Neoral blood levels were superior to that in Sandimmune and reached statistical significance. There were no safety concerns regarding the Neoral in the pediatric kidney transplant population.

GB-03 study: Neoral in pediatric kidney transplant patients

UK randomized, open-label, prospective, single-center, six-month pilot study was to compare PK, efficacy and safety of Neoral in de novo pediatric renal transplant recipients. Study design: initial oral dose of Neoral at a dose of 5 mg/kg, administered either prior to transplantation or within 12 hours post transplant. Patients were clinically assessed on the days 0 (day of transplantation), 1, 5, 14, and at weeks 4, 13 and 26. 12-hour PK post transplant profiles were measured on days 5, 14, and at weeks 4, 13 and 26. CyA assays were done on whole blood using enzyme immunoassay EMIT.

32 children were enrolled into the study and 29 completed the PK analysis with 110 PK profiles collected over the study period. A median age was 10.3 years (3 – 18 years), 9 were below 6 years of age; 8 were between 6 and 11, and 15 were from 11 to 18 ys.

Within the 6 months period 13 patients experienced clinical rejection (41%), half of them were biopsy-proven. All but two rejection episodes were corticosteroid sensitive and 2 grafts were lost due to acute rejection (1 graft due to renal artery thrombosis).

Mean CyA exposure (AUC₀₋₁₂) increased from 5385 ng.hr/mL at day 5 to a maximum of 6546 ng.hr/mL at day 14, falling to 3798 ng.hr/mL by week 26. Absorption (AUC₀₋₁₂ per mg/kg dose) of Neoral CyA increased with increasing age. The lowest was children < 4 ys (60%), in the year group 4–8 reached 70%, 77% in the year group 9–12 and the highest (96%) in the year group 12–16. C₂ levels correlated better with AUC₀₋₁₂ than C₀ in all age groups and at all time points studied. The day 5 mean C₂ level was lower in patients who experienced rejection: 960 ng/mL vs 1220 ng/mL in patients without rejections

($p=0.052$). Patients who reached C2 level of PK profile on day 5 above 1500 ng/mL ($n=6$) did not experience any rejection episode. In contrast patients with $C2 \leq 1500$ ng/mL ($n=22$) experienced acute rejection in 50% ($p<0.05$). No correlation was found between C2 levels and serum creatinine, GFR, or AEs in this study.

No patients died. 6 patients previously quit the study before the 6 months period (3 due to graft loss, 3 due to the switch in immunosuppressive treatment). Infections appeared in 20 children (62.5%), 4 of them had CMV infection.

➤ **Assessors comment:**

There is an increase in exposure over the first 2 post transplant weeks with a subsequent stabilization within the 24 weeks. CyA absorption increases with the age and C2 level is more closely predictive of acute rejection risk and gives more precise information regarding CyA absorption compared to C0 in pediatric kidney transplant population.

Clinical studies in non-transplant indication

OLO9510 study: CsA (Sandimmun) in the treatment of nephrotic syndrome in adults and children with steroid resistant nephropathy with minimal histological lesions or focal and segmental glomerulosclerosis

Open-label, multicenter, prospective, parallel group study in children and adults suffering from steroid-resistant idiopathic nephrotic syndrome (NS). Study design was to compare the efficacy and safety of CyA in induction of remission with the supportive therapy.

45 patients with steroid-resistant INS were randomized either to control group ($n=12$ adults/7 children), or to supportive therapy or to CyA for six months ($n=12$ adults with the dose of 5 mg/kg/day; $n=10$ children with the dose of 6 mg/kg/day), and then tapered off by 25% every two months until complete discontinuation.

Within the first year 13/22 CyA treated patients vs 3/19 controls reached the remission ($p<0.001$). The mean symptom score assessed at time 0 and at 6 months significantly decreased in the CyA group ($p<0.001$), but remained unchanged in the control group. Within the first treatment year 4/10 children reached complete remission, 2/6 children had partial remission. The variability between children and adults were of no influence.

Mean proteinuria, serum proteins and plasma cholesterol improved significantly in the CyA treated group at month 6, but did not change in the control group. No significant differences in renal function (serum creatinine, GFR) were found between treatment groups ($p=0.089$) and basal ($p=0.935$). Side effects were mild and no differences in side effects were even found between adult and children groups.

➤ **Assessors comment:**

CyA treatment resulted to the remission in 60% of adults as well as children suffering from steroid resistant idiopathic NS. CyA at this therapeutic scheme was not nephro and extrarenal toxic in patients with normal renal function and severe hypertension was not observed.

OLO9511 study: CsA (Sandimmun) in the prevention of relapses of steroid-dependant nephrotic syndrome in adults and children

Italian open, multicentre, prospective, randomized, controlled study to compare the efficacy (to achieve remission), safety and tolerability of CyA with cyclophosphamide in patients with steroid dependent or frequent relapses of nephrotic syndrome (NS) in induction of remission. Study design: parallel groups, stratified for adults and children.

73 patients suffering from steroid sensitive idiopathic NS were randomly assigned to either for 8 weeks of cyclophosphamide (2.5 mg/kg/day) or for 9 months CyA (adults with the dose of 5 mg/kg/day, children 6mg/kg/day), tapered off by 25% every month until complete discontinuation at month 12. 7 patients were lost to follow-up. The remaining 66 patients were followed-up for 3-24 months. 55 enrolled patients were children. 30/55 patients were randomized to the CyA treatment group, 25/55 to the cyclophosphamide group.

At month 9, in CyA treated group: 26/35 were in complete remission, 5/35 were in partial remission; in cyclophosphamide treated group 18/28 were in complete remission, 1/28 in partial remission. The risk of relapse was similar between frequent relapsers (19/22) and steroid dependent patients (8/14) on CyA and 5/15 in frequent relapsers and 6/15 in steroid dependent patients on cyclophosphamide. The number of relapses/year and the mean dose of prednisone/year were significantly lower ($p < 0.001$) in both treatment groups compared with the year prior to randomization. At year 2, on CyA 25% of patients (50% adults and 20% children) and 63% on cyclophosphamide (40% adults and 68% children) were without any relapse of NS. The tolerance of both active substances was generally good.

➤ **Assessors comment:**

Both, CyA and cyclophosphamide treatments are effective, well tolerated; there were more patients on cyclophosphamide having stable remission. The CyA related side effects were mild and disappeared after CyA discontinuation. No differences between adults and children were seen with either treatment.

OLR351 study: CsA in juvenile rheumatoid arthritis-phase IV post marketing surveillance study

Open, post-marketing observational study to review clinical efficacy and safety of CsA used for treatment of juvenile rheumatoid arthritis (JRA) or Juvenile idiopathic arthritis (JIA). Any juvenile patient with past or current treatments for JRA/JIA using CsA was eligible for inclusion in this study. Clinical data was completed at approximately every six month intervals. Children were divided in two arms depending on whether they were still receiving or had been discontinued from CsA. Study duration from January 1988 to May 2003.

Totally 319 children (from Europe and USA) were analyzed. Patients receiving CsA – 713 visits, patients after CsA therapy discontinuation - 527 visit.

Mean age of children when CsA therapy was initiated was 11.5 ± 5.5 . Overall, 23% of subjects received CsA for less than 6 months and 34% received CsA for greater than 24 months. The mean CsA dose was 3.4 mg/kg/day. Concurrent therapy was methotrexate in 61% of subjects; and prednisone in 65% of subjects.

A complete clinical response was documented in 13 patients (9%); moderate or severe disease was in 93 patients (61%). Eleven percent reported resolution of side effects after discontinuation of CsA.

➤ **Assessors comment:**

This post-marketing survey has only limited data. Therefore, for purpose of clarification of the role of CsA in JIA treatment a randomized controlled trial would be justified.

3. Discussion on clinical aspects

The results of 8 clinical pharmacology studies, 3 clinical studies in transplantation and 3 clinical studies in non-transplant indication, which are reviewed in this survey, are in agreement with current Core Data Sheet and support efficacy and safety of both Neoral and Sandimmun in approved indications in pediatric population.

Therefore no amendments to current SmPC and PIL are recommended.

Pharmacovigilance aspects:

The two last PSURs (the twelfth PSUR covering the period from 01 Jan 2006 to 31 Dec 2006 and the thirteenth PSUR covering the period from 01 Jan 2007 to 31 Dec 2009) were reviewed for information regarding safety in paediatric population.

According to MAH there is no evidence that the safety profile of Sandimmun /Sandimmun Neoral is different in children from that expected for the drug. Aside of risks described in the Core Data Sheets, within the twelfth PSUR there is no new evidence of any specific risk in other special patient groups.

Within the thirteen PSUR no significant new information on the experience in special patient groups was identified during the review period. An analysis of the age groups presented in adverse event reports was provided with the comment that the analysis did not reveal any specific issue with regard to specific age groups, including use in the paediatric population.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

V.1 Overall conclusion

The knowledge acquired from reports and publications submitted by the company is well in line with current Summary of Product Characteristics and Patient Information Leaflet, children from 1 year of age have received Sandimmun in standard dosage with no particular problems, paediatric patients required and tolerated higher doses of Sandimmun than adults. There was no new significant safety information revealed in PSURs submitted to member states.

No amendments to product information are proposed by the marketing authorisation holder and reference member state is in agreement.

V.2 Recommendation

No further regulatory action is required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Novartis Sandimmun 100 mg soft gelatin capsule

Novartis Sandimmun 25 mg soft gelatin capsule

Novartis Sandimmun 50 mg soft gelatin capsule

Novartis Sandimmun 10 mg soft gelatin capsule

Novartis Sandimmun 100 mg/ml oral solution

Novartis Sandimmun 50 mg/ml concentrate for solution for infusion

Novartis Sandimmun Neoral 100 mg soft gelatin capsule

Novartis Sandimmun Neoral 25 mg soft gelatin capsule

Novartis Sandimmun Neoral 50 mg soft gelatin capsule

Novartis Sandimmun Neoral 10 mg soft gelatin capsule

Novartis Sandimmun Neoral 100 mg/ml oral solution

Novartis Sandimmun Neoral 50 mg/ml concentrate for solution for infusion

The comments were received from the UK and HU on day 85 of the procedure; both member states endorsed the rapporteur's recommendations and had no further comments.