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Original Paper

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The efficacy and safety of ciclosporin (Equoral®) capsules after renal transplantation: A multicentre, open-label, phase IV clinical trial

Magdalena Durlik[1], Leszek Pączek[2], Bolesław Rutkowski[3], Dorota Lewandowska[1], Alicja Dębska-Ślizień[3], Andrzej Chamienia[3,4], Janusz Wyzgał[5], Anna Ognista-Gajda[1], Mariusz Niemczyk[2]

[1] Department of Transplantation Medicine and Nephrology, Medical University of Warsaw, Warsaw, Poland
[2] Department of Immunology, Transplantology and Internal Medicine, Medical University of Warsaw, Warsaw,Poland
[3] Department of Nephrology Transplantology and Internal Medicine, Medical University of Gdansk, Gdańsk, Poland
[4] Department of General Nursing, Chair of Nursing, Medical University of Gdańsk, Gdańsk, Poland
[5] Department of Nephrological Nursing, Medical University of Warsaw, Warsaw, Poland

Summary

Background: The use of bioequivalent generic ciclosporin is a cost-effective alternative to non-generic ciclosporin in renal transplant patients. This study aims to explore the efficacy, safety and tolerability of Equoral®, a generic ciclosporin, in adult *de novo* renal transplant patients.

Material/Methods: This was a multicentre, open label, phase IV clinical study consisting of a 6-month treatment and 3-month follow-up periods. Patients underwent renal transplantation supported by an immunosupressive regimen of azathioprine (or mofetil mycophenylate [MMF]), prednisolone and Equoral® (10 mg/kg/day, given 12 hours before patients' surgical procedure, and a maintenance ciclosporin dose of 4–6 mg/kg/day thereafter). The primary endpoint was the rate of occurrence of acute graft rejection over the 6-month period after renal transplantation.

Results: A total of 54 patients were enrolled and constituted the intention-to-treat/safety population, while 52 patients forming the per-protocol population were assessed for efficacy. There were 13 episodes of acute graft rejection reported in 12 patients, and two of these episodes resulted in withdrawal from the study. The probability of acute rejection in patients was less then 24% for the duration of the study including the observation period which is within the usual range. There were no deaths and one graft loss during the study, and the safety and tolerability profile reported was typical of that of ciclosporin in use in *de-novo* renal transplant patients.

Conclusions: The use of the generic ciclosporin Equoral® is effective and is associated with the usual safety and tolerability profile of ciclosporin when used as the calcineurin-inhibitor component of an immunosuppressive regimen in *de novo* renal transplant patients.

Key words: **ciclosporin • generic drugs • renal transplantation**

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Author's address: Magdalena Durlik, Nowogrodzka 59 Str, 02-006 Warsaw, Poland, e-mail: mdurlik@wum.edu.pl

Background

The use of ciclosporin in transplant patients heralded the modern age of solid-organ transplantation, increasing both graft and patient survival [1]. Moreover, despite the introduction of newer immunosuppressants, the use of calcineurin inhibitors such as ciclosporin or tacrolimus incorporated into immunosupressive regimens remain the proven standard of car [2,3]. The original oil-based oral formulation of ciclosporin (Sandimmun®) was characterised by widely varying bioavailability and pharmacokinetics – both within the same patient and between different patient [4,5]. Intra-individual variability, in particular, is a critical issue associated with acute and chronic graft rejection [6]. As such, Sandimmun® has largely been superseded by a microemulsion formulation (Neoral®) that circumvented these problems and consolidated ciclosporin's position as the mainstay immunosupressive therapy in all types of solid organ transplantation [3–5].

The cost of generic immunosuppressive agents is, however, particularly important for transplant patients: life-long maintenance immunosuppression is generally required to prevent renal transplant rejection, and this is associated with a substantial financial cost per patient [7,8]. The high cost of immunosuppressive maintenance therapy may also contribute to a lack of compliance with prescribed medical regimens, and thus the introduction of lower-cost generic versions may improve patient outcomes in some healthcare environments as well as lowering treatment costs [8]. It is vital, however, that generic products are both pharmaceutically equivalent and bioequivalent to well-established original drugs. This is a particular challenge for ciclosporin as it has a narrow therapeutic index and pharmacokinetics which are non-linear and highly variable between individuals [6]. Nevertheless, if bioequivalence is proven according to European and/or US bioequivalence guidelines, then original and generic ciclosporin formulations should generally be equivalent with regard to clinical benefits and risks [6,8].

A patented soft gelatin capsule (SGC) formulation of ciclosporin has been developed (Equoral® SGC; IVAX Pharmaceuticals, Miami, Florida, USA) and approved by regulatory authorities [9]. Bioequivalence of Equoral® and Neoral® capsules were proven following single-dose comparative studies for both formulations in healthy volunteers [10] and steady-state pharmacokinetic studies in which stable adult renal transplant patients switched from Neoral® to Equoral®, demonstrating equivalent pharmacokinetics with the two ciclosporin formulations [9,11]. It is desirable, however, to conduct longer-term studies to check the potential clinical benefits of Equoral®. To this effect, a small, 6-month study in *de novo* renal transplant patients (n=10) has shown patient and allograft survival rates of 100% [12]. Thus, the present study investigates clinical outcomes in larger number of renal transplant patients given Equoral® during a 9-month period after transplantation.

Material and Methods

Study design and patients

This was a multicentre, open label, phase IV clinical study which was designed to evaluate the efficacy and safety of Equoral® capsules after *de novo* renal transplantation in adult recipients, consisting of a 6 month treatment period and 3 months of follow-up. The protocol was conducted according to the Declaration of Helsinki (1964) and its subsequent amendments and revisions as well as Good Clinical Practice guidelines, and was approved by local independent ethics committees. Patients who gave their written, informed consent were recruited from three centres in Poland (2 in Warsaw; 1 in Gdansk).

Patients were invited to participate if they were aged between 18 and 65 years and about to undergo a planned *de novo* renal transplantation from either a cadaveric or living donor. Additional inclusion criteria were: no history of alcohol or drug abuse or signs of alcohol-induced organ damage; no history of a malignancy or significant infection, or sign of active hepatitis; normal blood pressure on antihypertensive treatment; able to communicate freely with the study investigators and to comply with the study procedures. Exclusion criteria included: a history of hypersensitivity to ciclosporin or related products, gastrointestinal illness or other illness that could affect the absorption or pharmacokinetics of ciclosporin, recent myocardial infarction or uncontrolled arrhythmia; uncontrolled hypertension; multi-organ transplant (more than one kidney); pregnant or lactating women or pre-menopausal women of childbearing potential who were not using safe contraception (abstinence was allowed); exposure to drugs that interfere with ciclosporin pharmacokinetics; patients with significant medical problems or unstable disease states.

Treatments

The initial ciclosporin dose of 10 mg/kg/day (given as two doses) was administered 12 hours before patients' surgical procedure, and a mmaintenance ciclosporin dose (4–6 mg/kg/day, given as two doses) was given thereafter, adjusted to maintain whole blood ciclosporin trough levels between 200–300 ng/mL. Ciclosporin was given as part of a triple regimen in combination with azathioprine (or mofetil mycophenylate [MMF]) and prednisolone. Intravenous (i.v.) prednisolone was given as follows: 500 mg (day 1), 250 mg (day 1), 125 mg (day 2), and then prednisolone tablets (0.5 mg/kg/day) from day 3 until 2 weeks after the transplantation, tapering thereafter to 15 mg/day at the beginning of the third month, and to 10 mg/day at 6 months. The initial azathioprine dose of 150 mg/day at day 0 was adjusted within the range 100–150 mg/day thereafter according to patients' neutrophil counts. A change from azathioprine to MMF capsules, 750–1000 mg twice daily, was permitted in cases of neutrophil depletion or because of lack of effect of azothioprine. If acute rejection occurred, the protocol specified i.v. methylprednisolone, 500 mg, for 3 days. In cases of steroid-resistant acute rejection, investigators could continue with methylprednisolone or administer a rabbit antihuman thymocyte globulin preparation or other approved monoclonal antibodies, given according to manufacturers' recommendations. Acute rejection episodes were diagnosed by the presence of the following criteria and according to the proposed consensus for definitions and endpoints for clinical trials of acute kidney transplant rejection: increase of creatinine in excess of 29 µmol/L or 30% over baseline; exclusion of other causes of renal function impairment (i.e., drug toxicity, cytomegalovirus infection, dehydration, mechanical obstruction); and biopsy-proven episodes [13]. A kidney biopsy was performed according to an investigator's recommendation or request at any time during the trial, but was mandatory if acute rejection criteria outlined above were fulfilled. The use of additional concomitant medications was permitted, and recorded in case report forms, although if known to interfere with the activity of cytochrome P450 (CYP) 3A4, bile metabolism or gastric emptying, then additional trough blood ciclosporin levels were determined and, if necessary, adjustments of ciclosporin doses were made to keep concentrations within pre-specified target blood levels.

Monitoring, assessments and endpoints

The primary study objective was to evaluate the efficacy of Equoral® capsules, whilst the secondary objectives were to ascertain the safety and tolerability of Equoral® capsules, as performed in *de novo* adult renal transplant patients. Specifically, the primary endpoint was expressed as rate of occurrence of acute graft rejection over the 6-month period after renal transplantation. Secondary endpoints consisted of the number of patient deaths and graft losses; daily doses of ciclosporin and number of dose adjustments; trough ciclosporin blood levels; laboratory values and serum creatinine levels; blood pressure and vital signs; adverse events and quality-of-life assessments (Short Form [SF]-36). The sequence and timing of study events, including screening, hospitalization and monitoring of efficacy and safety, were conducted as outlined in Table 1.

All patients underwent a screening visit before they were hospitalized (day 0 of the study) for their transplant procedure, and if the aforementioned criteria for inclusion were met and the exclusion criteria were not fulfilled then they were allowed to enter the study. The hospitalization period after transplantation was left to individual investigator's discretion. Patients returned to the study centers at weeks 4, 7, 10, 13, 19, 24 and 36 after hospitalization when the following were assessed: ciclosporin trough levels, serum creatinine, blood pressure, laboratory parameters, vital signs, adverse events, rejection episodes, clinical symptoms and tolerability.

Safety assessments included the monitoring of vital signs: body weight; systolic and diastolic blood pressure (measured once always using the same arm by a trained nurse with a mercury sphygmomanometer in patients after sitting quietly for 5 minutes); radial pulse rate after 5 minutes sitting, measured manually by a trained nurse at the same time as blood pressure; body temperature. All adverse events, including observed, elicited or volunteered problems, complaints or symptoms, were recorded. Each adverse event was evaluated by the study investigator for date of onset, duration, intensity (mild, moderate or severe), seriousness and causal relationship with study drug (e.g., definite, probable, possible, not assessable or none). All adverse events were followed up by study investigators until the events resolved.

Statistical analyses

Statistical analyses were performed using SAS® software. Two populations were defined. The

Table 1. Outline of sequence and timing of study events, including screening, hospitalization and monitoring of efficacy and safety.

	Screening	Hospitalization	Treatment period						Follow-up period
Visit			1	2	3	4	5	6	7
Day	0	0–14 (35)							
Week (after hospitalisation)			4	7	10	13	19	24	36
Informed consent	X								
Patient selection criteria	X								
General medical history	X								
Demographic data	X								
Physical examination, including vital signs	X	1, 3, 7 day and then every week	X	X	X	X	X	X	X
Haematology, biochemistry, urine chemistry	X	Every week, X	X	X	X	X	X	X	X
Pregnancy test (urine or blood)	X								
Ciclosporin blood trough level	X	Every week	X	X	X	X	X	X	
Drug dispensing		At hospital discharge	X	X	X	X	X	X	
Adverse events assessment		Daily	X	X	X	X	X	X	X
Concomitant medication	X	Daily	X	X	X	X	X	X	X
Quality of life assessment	X		X					X	X

intent-to-treat (ITT) population consisted of all patients who received at least one dose of study medication whilst the per-protocol (PP) population comprised of all ITT patients excluding those who incurred a major protocol violation (defined as an event or behaviour of the patient or the investigator which makes the evaluation of the patient impossible or unreliable). Regarding the primary endpoint, rejection episodes were analysed on the ITT population using survival statistics including Kaplan-Meier curve estimation of probability of an occurrence of acute rejection. Changes in variables from baseline throughout the study were analysed by two-sided parametric and non-parametric tests (Student's t-test and Wilcoxon test where appropriate) according to normal or non-normal distribution of variables verified by Shapiro-Wilk test. *P* values less than 5% were considered statistically significant. Demographic characteristics at baseline, drug blood levels, number of dose adjustments, daily doses of ciclosporin, incidence of adverse events, laboratory variables and changes of these variables were presented using descriptive statistics (mean, standard deviation, median, minimum and maximum) and analyzed using parametric (paired and non-paired Student's t-tests) or non-parametric tests (Wilcoxon rank-sum tests, if data did not meet the assumptions required for normality). The relationship between the analysed variables was estimated by Pearson-Spearman coefficients of correlation and by analysis of linear regression.

Results

Patient disposition

Patient recruitment started in May 2004 and ended in December 2005. A total of 54 patients were enrolled. As they all gave their informed consent and received at least one dose of ciclosporin, the ITT population thus consisted of 54 patients. The baseline demographic characteristics for the ITT population are shown in Table 2. The main causes of renal failure were glomerulonephritis (19 of 54 patients; 35.2%), uropathy (6 patients; 11.1%), polycystic disease (6 patients; 11.1%) and congenital nephropathy (4 patients; 7.4%). The most common concomitant active disease reported

Table 2. Baseline demographic characteristics for the intention-to-treat (ITT) population (n=54). Data are presented as number(percentage) unless otherwise specified.

Characteristic	
Sex, male	37 (68.5%)
Race, Caucasian	54 (100%)
Mean age, years	42 years (SD 9.92; range 23–61 years)
Mean cold ischaemia time, hours	21.8 hours (SD 10.0; range 0–38.5)
Mean number of HLA mismatches*	3.1 (SD 0.86; range 2–5)
Donor type:	
Cadaveric	53* (100%)
Living	0 (0%)

HLA – human leukocyte antigen. * One patient in the ITT population (n=54) did not undergo a kidney transplant procedure.

Table 3. Patient withdrawals from the study.

Reason for withdrawal	Number (%) of patients
Screening failure/violation of entry criteria:	
Pregnancy before the study	1 (12.5%)
History of malignancy before the study	1 (12.5%)
Withdrawal according the protocol:	
Acute rejection episode	2 (25.0%)
Insufficient response to treatment	2 (25.0%)
Patient ineligible to continue treatment	1 (12.5%)
Other	1 (12.5%)

at patients' screening visit was hypertension (47 patients; 87.0%), anemia (39 patients; 72.2%), cardiomyopathy (8 patients; 14.8%), hyperlipidaemia (8 patients; 14.8%) and secondary hyperparathyroidism (6 patients; 11.1%).

Two major protocol violations occurred. (One patient who was pregnant entered the study against the exclusion criteria, and received study medication but did not undergo a kidney transplant; one patient with history of malignancy entered the study against the exclusion criteria and was withdrawn from the study 7 weeks after hospitalization for transplantation.) Of the 52 patients who completed the study without major protocol violation (the PP population), 46 patients completed the entire course of the treatment as specified in the protocol and eight patients discontinued. Reasons for patient withdrawal are listed in Table 3.

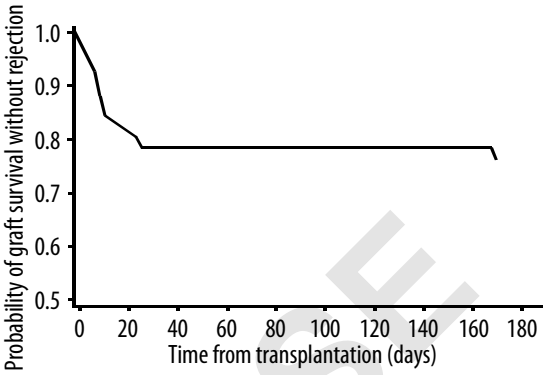

Figure 1. Kaplan–Meier curve estimation of probability of an occurrence of acute rejection.

Efficacy

The efficacy evaluation was performed for the 52 patients who completed the study or who withdrew from the study according to protocol. The primary endpoint of the trial was acute graft rejections in the first 6 months of the study and 13 of these episodes occurred in 12 patients. Twelve rejection episodes took place during the hospitalization period with the remaining episode occurring 169 days after transplantation. One prolonged steroid-resistant rejection episode was recorded as two separate episodes, and the remaining rejection episodes lasted between 4 and 11 days with a mean value of 6.5 days. In two cases treatment with methylprednisolone was ineffective and anti-thymocyte globulin (ATG) was given. Only two episodes of acute rejection resulted in the discontinuation from study procedures and premature withdrawal from the study of these two patients. The probability of graft rejection in patients after renal transplantation and treatment with Equoral® is less than 24% for the duration of the study including the observation period (Figure 1).

The mean daily dose of ciclosporin was 365 mg (364 mg in the 40 patients without a rejection episode and 369 mg in the 12 patients who experienced a rejection episode.) There was an average of 9.2 dose changes per 100 days' therapy (7.9 in the 40 patients without a rejection episode and 13.5 in the 12 patients who experienced a rejection episode.) There no were significant differences between the 'rejection' and 'no rejection' groups for mean daily dose or average number of dose changes, though there was a higher degree of variability in the rejection episode group (results not shown). Moreover, ciclosporin trough concentrations (C_0) were generally maintained

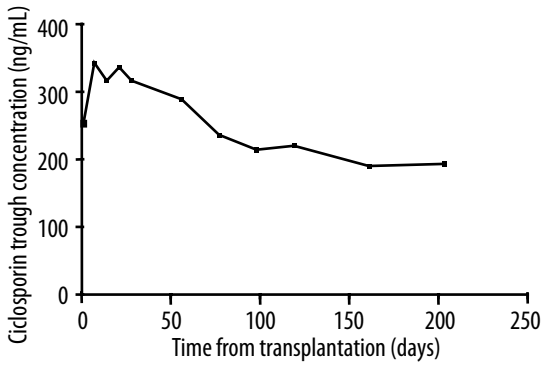

Figure 2. Mean ciclosporin trough concentrations (C_0).

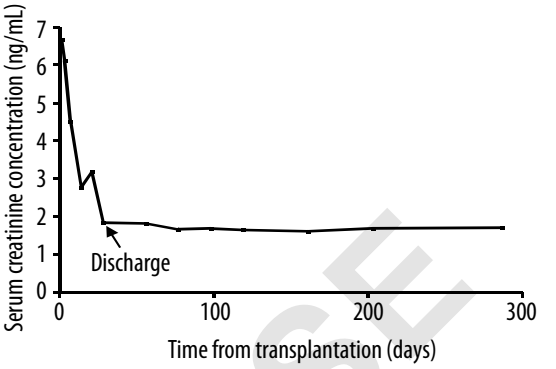

Figure 3. Mean serum creatinine levels.

Table 4. Mean ciclosporin 2-hour post-dose (C_2) and area under the curve (AUC) values at day 7 and day 14 after hospitalisation.

	N	Mean (ng/mL)	SD	Minimum (ng/mL)	Maximum (ng/mL)	Median (ng/mL)
Ciclosporin 2-hour post-dose (C2) concentrations						
Day 7	51	1191	452	268	2480	1205
Day 14	48	1306	492	326	2142	1345
Ciclosporin area under the curve (AUC) values*						
Day 7	43	3260	1118	1172	6030	–
Day 14	43	4050	1285	1722	6285	–

* The difference between AUC measured at day 7 and 14 was statistically significant (P=0.0260).

within target range (Figure 2). Ciclosporin 2-hour postdose (C_2) concentrations were also measured at day 7 and day 14 (mean values of 1191 and 1306 ng/mL, respectively) in addition to AUC values (Table 4). Note that the difference between AUC measured at day 7 and 14 was statistically significant (P=0.0260) but there was no corresponding significant difference for C_2 values.

Quality of life was measured using the SF-36 at screening and throughout the study. Whilst there was a general trend towards improved quality-of-life scores, the only significant improvements were in the SF-36 general health scale at 24 weeks and at 36 weeks *vs* the score at screening (P<0.0174 and P<0.0213, respectively).

Safety

Mean serum creatinine concentrations throughout the study are shown in Figure 3. This shows a rapid decline in serum creatinine levels following the transplantation to discharge, suggesting good kidney graft function. There were no statistical correlations between concentration of ciclosporin (parameters C_0 and C_2) and serum creatinine levels. Moreover, at the final follow-up visit, mean serum creatinine concentrations were very similar among patients with (n=9) and without (n=35) a history of graft rejection (1.66 and 1.73 ng/mL, respectively; P=0.61). There was no statistical correlation between the concentration of ciclosporin (parameter C_0) and the number of lymphocytes or patients' blood pressure. The results of other laboratory tests were generally as expected for renal transplant patients. For example, secondary anaemia typically developed after transplantation (as shown by haemocrit and, more importantly, haemoglobin levels [14] with patients recovering to levels approximately 80% of normal levels in healthy individuals. Serum uric acid and bilirubin levels tended to increase significantly (P<0.0001), though bilirubin levels remained within the normal range and increases in uric acid levels are a well-known effect of ciclosporin therapy [15].

A total of 587 adverse events were reported. Of these, 210 were assessed as being possibly, probably or definitely related to ciclosporin therapy and the remainder of adverse events were considered as not related (n=167) to the study drug or

Table 5. Serious adverse events, regardless of relationship with ciclosporin.

	Number of events	Number of patients	% of patients vs ITT population
Urinary tract infection	11	7	13.0
Hypercreatininaemia	10	10	18.5
Renal lymphocele	4	2	3.7
Complications of transplanted kidney	3	3	5.6
Intestinal obstruction	3	2	3.7
Renal vein thrombosis	3	1	1.9
Therapeutic agent toxicity	3	3	5.6

ITT – intention to treat (n=54).

Table 6. All non-serious adverse events occurring in at least 10% of patients, regardless of relationship with ciclosporin.

	Number of events	Number of patients	% of patients vs ITT population
Urinary tract infection	47	25	46.3
Anaemia	27	22	40.7
Hypertension	23	18	33.3
Hyperglyceridaemia	23	17	31.5
Hyperbilirubinaemia	18	14	25.9
Peripheral oedema	18	12	22.2
Hypercholesterolaemia	16	13	24.1
Upper respiratory tract infections	16	12	22.2
Hyperlipidaemia	15	15	27.8
Transaminases increased	14	11	20.4
Constipation	12	9	16.7
Hyperuricaemia	11	9	16.7
Hypertrichosis	9	9	16.7
Pyrexia	8	7	13.0
Renal lymphocele	6	6	11.1
Complications of transplanted kidney	6	6	11.1
Abdominal pain	6	6	11.1

ITT – intention to treat (n=54).

the relationship between the study drug and adverse event was not clear (n=210). There were 72 serious adverse events. The most frequent serious adverse events were urinary tract infections (11 of 72 events; 15.3%) and high creatinine levels (10 of 72 events; 13.9%) (Table 5). Amongst non-serious adverse events the most common were urinary-tract infections, anaemia, hypertension and hyperglyceridaemia (Table 6). There were no deaths during the study, though one patient who lost his graft and was withdrawn from the study died from sepsis 4 months later.

Discussion

The current study was designed to explore the efficacy and safety of the generic ciclosporin Equoral® in *de novo* renal transplantation. The results show that it appears to be both effective and associated with a reasonable safety and tolerability profile. One obvious drawback of the study design is that there is no comparator group, so it is not appropriate to speculate regarding comparisons of efficacy and safety of Equoral® with other ciclosporin formulations such as Neoral®.

Nevertheless, the present study extends the results of previous studies which were either conducted in healthy volunteers and comparing Equoral® and Neoral® [10] or were short-term Equoral®/Neoral® switching studies in renal transplant patients [9,11] or a longer term (6 month) noncomparative study in small numbers of renal transplant patients (n=10) [12].

The present study showed that the risk of an acute rejection episode was acceptable (less than 24% in the 9 months after transplantation) when Equoral® is used as a calcineurin inhibitor component of a standard immunosuppression regimen in renal transplant patients. Furthermore, there were only two acute rejection episodes in two patients that resulted in their withdrawal, one graft loss and no deaths during the study. Ciclosporin concentrations varied from patient to patient and required significant number of dose adjustments (7–25 dose changes for patients completing the trial), but no correlation was detected between the number of changes in dosage and occurrence of acute graft rejection. Furthermore, the immunosupressant regimen incorporating Equoral® in this study resulted in several well-known and previously described laboratory and clinical adverse events which reflect the severity of end-stage renal failure and the effects of ciclosporin regardless of formulation.

Conclusions

Thus, in conclusion, Equoral® appears to be effective with a predictable safety and tolerability profile typical of ciclosporin use in renal transplant patients. Whilst Equoral® has been approved in 10 European Union (EU) and 20 non-EU countries and has been proven to be bioequivalent to and switchable with Neoral®, a few doubts still remain concerning the use of bioequivalent generic ciclosporin in all groups of patients [8,16]. To address these concerns a further study such as a randomised, double-blind trial of Equoral® and Neoral® is desirable in a large population of renal transplant patients.

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