ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT / MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 25 mg	25 mg	capsule	oral use
Belgium		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 50 mg	50 mg	capsule	oral use
Belgium		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 100 mg	100 mg	capsule	oral use
Germany		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 25 mg	25 mg	capsule	oral use
Germany		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 50 mg	50 mg	capsule	oral use
Germany		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 100 mg	100 mg	capsule	oral use
Italy		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 25 mg	25 mg	capsule	oral use
Italy		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 50 mg	50 mg	capsule	oral use
Italy		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 100 mg	100 mg	capsule	oral use
Netherlands	IDL, 36 avenue Hoche 75008 Paris. FRANCE		Ciclosporin IDL 25 mg	25 mg	capsule, soft	oral use
Netherlands	IDL, 36 avenue Hoche 75008 Paris. FRANCE		Ciclosporin IDL 50 mg	50 mg	capsule, soft	oral use
Netherlands	IDL, 36 avenue Hoche 75008 Paris. FRANCE		Ciclosporin IDL 100 mg	100 mg	capsule, soft	oral use
Spain		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 25 mg	25 mg	capsule	oral use
Spain		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 50 mg	50 mg	capsule	oral use

Member State EU/EEA	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporina IDL 100 mg	100 mg	capsule	oral use
Sweden		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciklosporin IDL 25 mg	25 mg	capsule	oral use
Sweden		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciklosporin IDL 50 mg	50 mg	capsule	oral use
Sweden		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciklosporin IDL 100 mg	100 mg	capsule	oral use
United Kingdom		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 25 mg	25 mg	capsule	oral use
United Kingdom		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 50 mg	50 mg	capsule	oral use
United Kingdom		IDL, 36 avenue Hoche, 75008 Paris. FRANCE	Ciclosporin IDL 100 mg	100 mg	capsule	oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REFUSAL

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CICLOSPORIN IDL

Ciclosporin is a calcineurin inhibitor and as such an immunosuppressive drug. Ciclosporin is indicated in transplantation (e.g. prevention or treatment of rejection of solid organ transplantation, bone marrow transplantation, graft-versus-host-disease) and auto-immune diseases (e.g nephrotic syndrome, rheumatoid arthritis, psoriasis, atopic dermatitis).
The Reference medicinal product authorised in Germany is: Sandimmun Optoral 25 mg Kapseln.

Key results from the dossier supporting the MAA are reproduced below.

Variable	Fasting Point estimate (%) for test / reference (90% CI)	Fed Point estimate (%) for test / reference (90% CI)
$AUC_{(0\text{-}inf)}$ (ng.h.ml)	95.1 (92.2, 97.9)	109.6 (103.2, 116.3)
C_{max} (ng/ml)	88.2 (84.1, 92.4)	122.5 (108.9, 137.8)

In the MRP procedure (NL/H/1402/001-003/MR) potential serious risk for public health concern was raised on the following grounds: bioequivalence has not been sufficiently demonstrated.

The CHMP addressed a list of questions to the Marketing Authorisation Holder and to the Efficacy Working Party PK expert group for consultation on the following points:

1) The first issue raised by the CHMP was whether a normal (80-125%) or narrowed (90-111%) acceptance range should be applied for assessing bioequivalence under fasting conditions, considering ciclosporin is to be regarded a 'highly variable drug' with a Narrow Therapeutic Range.

The MAH answered that ciclosporin, in spite of being highly variable drug, is not to be considered a Narrow Therapeutic Index (NTI) drug because the clinical evidence for such a classification is lacking.

The classification of ciclosporin as an NTI drug could have been based on the adverse events associated with its use or on the concomitant use of other drugs.
The number of adverse events may be associated with the huge variation in blood concentrations of the reference drug that will follow if it is taken regardless of food intake and the lack of instructions given regarding food intake. This may result in major swings in blood concentrations, since it has been shown that the intake of food has a very negative effect on absorption (up to about 30% reduction of Cmax and 15% reduction in AUC) of the reference product. The effect of food on the blood concentrations, the large variation of the blood levels, and the resultant adverse events might well be other reasons for branding the reference product a NTI drug.

In the MAH view even if Ciclosporin was to be considered a NTI drug, the normal 80-125% acceptance range should be used.

The CHMP agreed with the EWP PK expert group position that if ciclosporin is considered a narrow therapeutic index drug, a narrowed (90-111%) acceptance range should be applied for AUC.
The CHMP acknowledged that a therapeutic index (TI) calculation has not been reported for ciclosporin but disagreed with the statement from MAH that it is based on the adverse events profile.
As ciclosporin is administered in high doses and for long periods of time in the clinical setting of transplantation, the CHMP refer to this indication for the justification of ciclosporin as being a NTI

drug. This justification is based on clinical judgments, both from an efficacy and safety point of view as follows:
- On the efficacy side not achieving therapeutic levels may lead to devastating consequences and therefore the SPC clearly states that monitoring blood levels are essential during treatment with ciclosporin and when switching to another formulation.
-The safety profile of ciclosporin is also critical. It is essential the therapeutic monitoring of renal, liver functions and blood pressure as adverse events are reported as very common and in a transplant population can be clinically devastating.

2) The second question raised by CHMP was whether the same acceptance range (either normal or narrowed) should be applied both for AUC and Cmax.
The MAH answered that there doesn't seem to be a convincing reason why the range (80-125%) should be different for Cmax and AUC. Differences in Cmax were considered less important, because a peak level is maintained for only a short period of time, whereas AUC represents the total exposure to the drug, but it was felt that the conventional range should be used.

The CHMP considered that as ciclosporin is NTI drug, narrowing the Confidence Interval (CI) range to 90-111%, would minimize the risk of over or under exposure. For generic applications no other data than bioequivalence is assessed and therefore approval should be based with confidence that such risk is reduced at maximum by narrowing the CI. This narrow range should apply to both AUC and Cmax as outside range values for any of both parameters can lead to efficacy and/or safety unwanted consequences.

In the 'fasting' bioequivalence trial presented, the 90% confidence interval for Cmax does not meet the tighter 90-111% acceptance criteria.

3) The third point raised by CHMP was whether the same set of requirements should be applied for assessing bioequivalence under high-fat fed conditions.
In the MAH view the same set of requirements should usually be applied in the case of studies under high fat fed conditions. For ciclosporin IDL, it was argued that because the differences observed between test and reference products under fed conditions were not due to the test product, but to the very profound effect of food on the blood levels of the reference product, no safety concern arose and the upper 90% confidence limit for comparison of Cmax (137%) was acceptable (see 4 below).

The EWP PK expert group advised that since ciclosporin may be given either with or without food, the requirements with regard to bioequivalence should be the same in both fasted and fed states. CHMP concluded that the bioequivalence data observed were inadequate to establish efficacy and safety. In particular the upper confidence limit for the comparison of Cmax was outside even the standard acceptance range.

4) The fourth issue raised by CHMP was about the food effect on ciclosporin.
The SPC for Sandimmun Optoral allows administration regardless of food, indicating that the known food effect for ciclosporin (approximately 26% reduction of Cmax and 15% reduction of AUC) is considered not clinically relevant. Taking this into account, the question was whether a reduced effect of food on generic ciclosporin pharmacokinetics could be considered acceptable for a 'generic application', even in case that this results in a failure to comply with the predefined acceptance criteria (e.g. 80-125%) for concluding bioequivalence under fed conditions (in this case with a 90% CI for Cmax of 1.09-1.37).

The MAH answered that the reduced effect of food on generic ciclosporin pharmacokinetics as compared to the innovator formulation could be seen as an advantage over the reference product and a compelling argument for the acceptance of the former. In addition, in the Transplant Patient Guide (University of Southern California-Cardiothoracic Surgery and Pancreas Transplant Program), it is recommended to take ciclosporin before meals, for better absorption by the stomach. In clinical routine practice therapeutic drug monitoring is done in order to control for and monitor safety.

The Efficacy Working Party PK expert group, consulted by the CHMP, understood that in clinical practice, ciclosporin is often recommended to be taken in a standardised way in relation to food. They therefore advised that a generic ciclosporin product should be bioequivalent with the originator product both in the fasting and in the fed state.

The CHMP acknowledged that the food effect seen on Ciclosporin IDL is lower then the effect on the innovator and that it may represent an advantage for a product that can be administered with or without food. However, in the absence of other data, it is not possible to confirm that under fed conditions the test product is bioequivalent and therefore will have the same efficacy and safety profile of the innovator.

The procedure included an oral explanation, at which the MAH presented their views that:
- clinical evidence-based classification of Ciclosporin as a NTI drug was still lacking, difficult to calculate, and based only on the adverse events for which an explanation was already given,
- the 90% CI relates to the population effects, whereas in clinical practice the substantial intra-individual variability is critical for the variable ciclosporin blood levels and this is the reason why it is monitored by frequent plasma through concentration even with the brand leader and these determinations which are routinely performed will allow to correct immediately deviation of the 10% or 20%.
There is emerging data indeed to suggest that appropriate therapeutic monitoring may radically reduce the incidence of acute rejection in de-novo recipients and ameliorate chronic rejection and secondary effects in maintenance transplant patients, as for ciclosporin, the patients inter and intra-variability is actually more problematic than the therapeutic index.

The CHMP, after the oral explanation, found that the data and the justification presented were not adequate to confirm the bioequivalence between the test and the originator.

The CHMP maintained its conclusion that bioequivalence of Ciclosporin IDL to the originator has not been adequately demonstrated, either in fed or fasted conditions.

RE-EXAMINATION OF THE CHMP OPINION ADOPTED ON 23 APRIL 2009

Summary of Grounds for Re-Examination
The MAH decided to appeal, and triggered a re-examination of the CHMP opinion on the following grounds:
In view of the MAH, from the data generated by the bioequivalence studies, the ciclosporin test product is in the range 90%-111% for the AUC and less than 111% of the reference for the Cmax in the fasted conditions study which reflects the pharmacokinetic parameters without any interaction. The other study in fed conditions showed that Ciclosporin IDL was less affected by food than Novartis Neoral reference product. The MAH stated that this issue needs to be addressed by the Regulatory Authorities and should be taken into consideration when evaluating IDL test product formulation, because this could play a definite role for safety issues, knowing that efficacy was preserved in any case as shown by the AUCs results.
The MAH divided its argumentation into 2 parts: bioequivalence and safe switch, and pharmaceutical properties of Sandimmune Optoral and Ciclosporin IDL micro emulsions

Bioequivalence and safe switch
The MAH quoted a publication from *The National Kidney Foundation* of 1999 raising inequivalence concerns for transplant organ immunosuppressants and introduced the term “critical-dose drug”. The authors considered both cyclosporine and tacrolimus to be critical-dose drugs.
The MAH noted that the SPCs of Sandimune and Neoral state that these two products are not bioequivalent, but a switch between these products is allowed with an appropriate therapeutic drug monitoring (TDM), indicating that this is well established common practice blood concentration guided dosing of ciclosporin.

The CHMP considered that similar argumentation (using TDM) must not be used to excuse any failed bioequivalence for any generic product. A generic product should be possible to use interchangeably with an originator product without taking any extra measurements. The issue here is clearly not a problem of interchangeability between Sandimmune and its optimized formulation of Neoral, but a lack of proof of bioequivalence, since this is a generic procedure.

Bioequivalence in fast conditions
In the case of Ciclosporin IDL, the MAH argued that bioequivalence has been proven in the fasting state in CI (80-125%). The upper 90% interval confidence limit for $C_{max,}$ which should be considered for safety issues, is below the accepted limit (111%) for NTI products. The MAH claimed that these results showed efficacy equivalence without safety issues in fast conditions.
The CHMP did not agree upon the lack of safety concerns in fasting conditions and did not endorse the use of asymmetric CIs. The CHMP concluded that bioequivalence has not been demonstrated in fasting conditions. Further, the MAH did not submit any data showing that Cmax values outside the bioequivalence criteria do not change the efficacy/safety performance of the product in comparison to the reference product.

Bioequivalence in fed conditions
The MAH also stated that bioequivalence under fed conditions has not been shown, since the PK of Ciclosporin IDL formulation is considerably less affected by food than the reference product.
The CHMP in principle agreed that a decreased sensitivity of the ciclosporin absorption to food intake could be seen as an advantage, however a generic product should be bioequivalent and possible to be used interchangeably with an originator product based on bioequivalence and this has not been demonstrated.
The CHMP considered also the data the MAH submitted for PK simulations of ciclosporin concentrations for both reference and test product repeated dosing in fed and fasted states. The data showed that the variability with each formulation between fed versus fasted is much lower for the test then for the reference drug, although the area under the curve is not much different.

The MAH stated that in the particular case of ciclosporin, and because of inter-subject variability, the monitoring of blood concentrations is the most important criterion to prevent from any public health issue.

The CHMP noted that MAH stressed the need for routine TDM and from experienced physicians to prescribe ciclosporin, but these arguments could not counterbalance any failed bioequivalence for any compound being proposed as generic of the reference product.

Pharmaceutical properties of Sandimmune Optoral and Ciclosporin IDL micro emulsions

The MAH summarized previous studies showing that the size of the emulsion droplets and concomitant food intake have an effect on the absorption of ciclosporin from the small intestine when orally administered, which may have an influence on the drugs' pharmacokinetic parameters The MAH compared Neoral and 3 batches of Ciclosporin IDL. As result, the size of the emulsion droplets of the test and the reference are comparable and the slight difference of the particles size could explain the lower impact of food on the intestinal absorption. Slightly smaller particles size of Ciclosporin IDL should be seen as an advantage for the absorption regarding food intake.

The CHMP considered that the size of the particles is not a relevant argument for accepting wider bioequivalence range for ciclosporin. Although this may be the explanation of the diminished food effect of the product, do not add any additional information with regard to Ciclosporin IDL possibly being approved as a generic bioequivalent to a reference product.

Benefit/risk assessment

Ciclosporin is considered a NTI drugs, and the MAH accepted this in the grounds for re-examination.
The data submitted showed that the 90% CI for Cmax fell outside the standard (80-125%) acceptance range in the fed state and outside a narrowed (90-111%) acceptance range in the fasted state and the respective value for AUC exceeds the narrowed acceptance range in the fed state.
The CHMP concluded that bioequivalence has not been satisfactorily demonstrated, the benefit/risk ratio is considered negative and Ciclosporin IDL cannot be recommended for approval.
Thus the CHMP retains its opinion and assessment report dated 23 April 2009 that the bioequivalence to the originator has not been shown and the benefit/risk ratio of Ciclosporin IDL is considered to be negative.
The CHMP adopted a final negative opinion recommending the refusal of the Marketing Authorisation in the Concerned Member States and the suspension of the Marketing Authorisation where the product is currently authorised.

GROUNDS FOR REFUSAL

Whereas

- the Scope of the Referral was about the bioequivalence (BE) of the generic Ciclosporin IDL to the originator.

Ciclosporin is considered a ‘critical dose drug’ with narrow therapeutic index. The evidence for bioequivalence, which meets narrow (90-111%) acceptance criteria for AUC under fasting conditions, meets standard (80-125%) acceptance criteria for Cmax in the fasted state, and fails to meet even standard acceptance criteria the fed state, is regarded as inadequate to support a conclusion of bioequivalence.

The CHMP has recommended the refusal of the granting of the Marketing Authorisations in the Concerned Member States and the suspension of the Marketing Authorisations for Ciclosporin IDL where the product is currently authorised.

ANNEX III

CONDITION FOR THE LIFTING OF THE MARKETING AUTHORISATIONS SUSPENSION

The RMS, the Netherlands, will assess data from a new bioequivalence study and, if the following condition is fulfilled and satisfactory data provided, the suspension of the Marketing Authorisations can be lifted:

The Marketing Authorisation Holder should conduct a new fasting and fed bioequivalence study showing the bioequivalence of Ciclosporin IDL under a tightened acceptance range (90-111%) for the 90% CI.