DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE MAY - 8 2000

Ronald G. Van Valen
Associate Director
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936

RE: NDA #50-715/50-716
Neoral (cyclosporine capsules and oral solution) MODIFIED
MACMIS ID #8415

Dear Mr. Van Valen:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a professional slide kit for Neoral (cyclosporine capsules and oral solution) MODIFIED, disseminated by Novartis Pharmaceuticals Corporation (Novartis), that violates the Federal Food, Drug, and Cosmetic Act and its implementing regulations. The professional slide kit, identified as NEO-3017, was submitted under cover of Form FDA 2253. DDMAC has reviewed this slide kit and determined that it promotes Neoral in a manner that is false or misleading. The slide kit contains misleading statements regarding bioequivalence and clinical effect.

The slide kit contains claims that misleadingly suggest transplant patients switched from Neoral to an "AB" rated generic cyclosporine product may not be kept within their therapeutic range. Several examples include:

- *"The slides in this in-service kit update suggest that different cyclosporine products, although approved within current regulatory bioequivalence guidelines, may not keep each transplant recipient within his or her narrow therapeutic range"*

- *"While the regulatory criteria for bioequivalence may be applicable for most drugs, they may not address some of the potential problems that can arise with critical-dose drugs, such as cyclosporine"*

- *"For critical-dose drugs, potential problems may occur when patients who have been stabilized on one product are inadvertently switched to another product without careful monitoring (ie, brand to generic, generic to brand, generic to generic)"*

Claims such as these, that suggest a lack of bioequivalence and clinical effectiveness for an "AB" rated generic equivalent are false or misleading.

At the time of dissemination of this slide kit, an "AB" rated generic equivalent was available for Neoral Oral Solution. All FDA approved dosage forms of generic drugs classified as therapeutically equivalent and coded AB can be substituted for the reference product with the full expectation that the substitutable products will produce the same clinical effect and safety profile.[1]

To address the violations specified in our letter, we request that you immediately cease distribution of these and other promotional materials for Neoral that contain the same or similar violations. Please submit a written response to DDMAC on or before May 23, 2000, describing your intent and plans to comply with the above. The response should also include a list of violative promotional materials and the dates discontinued.

If you have any questions or comments, please direct them to the undersigned by facsimile at 301-594-6771, or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

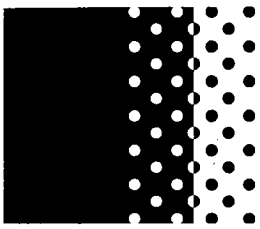
In all future correspondence regarding this particular matter please refer to MACMIS ID #8415 in addition to the NDA number.

Sincerely,

/S/

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

[1] According to the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through November 1999, drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.



In kidney, liver, and heart transplantation

Clinical Considerations for Substitution Between Cyclosporine Products

The slides in this in-service kit update suggest that different cyclosporine products, although approved within current regulatory bioequivalence guidelines, may not keep each transplant recipient within his or her narrow therapeutic range.

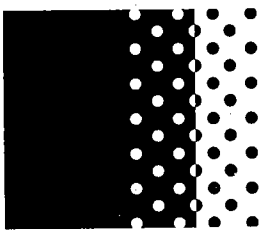
The key issues covered in this section of the in-service kit include:

- Current regulatory guidelines for establishing bioequivalence[1]
- Impact of formulation differences on cyclosporine pharmacokinetics in various patient subpopulations[2-4]
- Bioequivalence of different cyclosporine products based on mean data in healthy volunteers cannot ensure that certain patient subgroups will remain within their narrow therapeutic range[5,6]
- Specifying drug product is a good way to ensure that patients stay with the product on which they have been so carefully stabilized

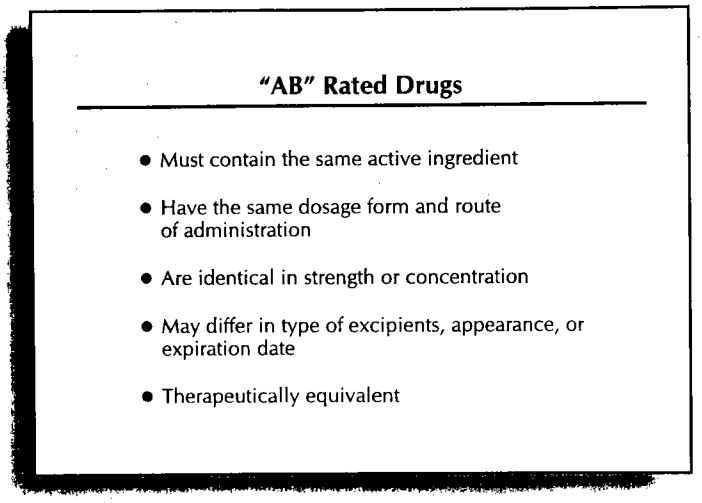
This section of your in-service kit will allow you to communicate an even more powerful rationale for writing "DAW."

NOT TO BE LEFT WITH PHYSICIAN. PLEASE PROVIDE FULL PRESCRIBING INFORMATION FOR NEORAL® (cyclosporine for microemulsion) AND SANDIMMUNE® (cyclosporine, USP).

References: **1.** Center for Drug Evaluation and Research. *Approved Drug Products With Therapeutic Equivalence Evaluations.* 17th ed. Rockville, Md: US Dept of Health and Human Services, Food and Drug Administration; 1997. **2.** Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit.* 1997;19:375-381. **3.** Chapman JR, O'Connell PJ, Bovington KJ, et al. Reversal of cyclosporine malabsorption in diabetic recipients of simultaneous pancreas and kidney transplants using a microemulsion formulation. *Transplantation.* 1996;61:1699-1704. **4.** Lindholm A, Welsh M, Alton C, et al. Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: racial differences in bioavailability. *Clin Pharmacol Ther.* 1992;52:359-371. **5.** Data on file, Novartis Pharmaceuticals Corporation. **6.** Curtis J, Van Buren DH, Pirsch J, et al. Lack of bioequivalence of two Sandimmune® (cyclosporine, USP) formulations in renal transplant patients who absorb cyclosporine poorly. Poster presented at: American Society of Transplant Physicians Meeting; May 9-13, 1998; Chicago, Ill. Abstract 249.



Slide 1



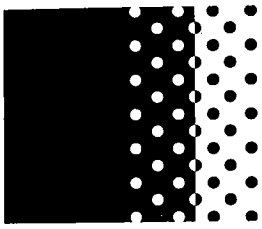
"AB" Rated Drugs

- To qualify for an "AB" rating, drug products must:
  - Contain the same active ingredient[1]
  - Have the same dosage form and route of administration[1]
  - Be identical in strength or concentration[1]
- However, formulations may differ in type of excipients (eg, preservatives or other inactive ingredients), appearance (eg, color, shape, scoring configuration), or expiration date[1]

Reference: 1. Center for Drug Evaluation and Research. *Approved Drug Products With Therapeutic Equivalence Evaluations.* 17th ed. Rockville, Md: US Dept of Health and Human Services, Food and Drug Administration; 1997.

Notes

Specify NEORAL® cyclosporine capsules and oral solution for microemulsion



Slide 2

Regulatory Guidelines for Determining Bioequivalence of "AB" Rated Drugs

Requires:	Does Not Typically Require:
• One positive study	• Multiple-dose, randomized crossover study design
• Single-dose comparison	• Efficacy/safety studies in patients
• Healthy volunteers	• Testing under actual clinical conditions
• A manufacturer-selected sample of the test drug	• Randomly selected test samples
• PK parameters that are between 80% and 125% of innovator product	• Individual data
• Mean data	• Subject by formulation interaction

Center for Drug Evaluation and Research. *Approved Drug Products With Therapeutic Equivalence Evaluations*. 1997. / Levy G. *J Pharm Pharmacol*. 1995;47:975-977.

Regulatory Guidelines for Determining Bioequivalence of "AB" Rated Drugs

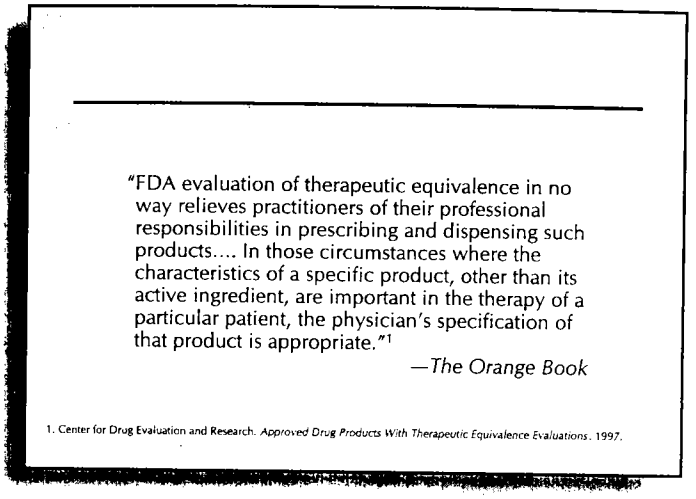
- The pharmacokinetic criteria for bioequivalence of "AB" rated drugs assess average or mean bioequivalence, not individual variability
- Typical bioequivalence studies are performed in 18 to 24 healthy male volunteers who receive a single-dose of the test drug under fasting conditions[1]
- For a test drug to be considered bioequivalent to the reference drug, 2 criteria must be met:
  - The rate and extent of absorption may not differ by more than −20%/+25%[1]
  - The 90% confidence interval for the ratio of the mean response (ie, area under the concentration-vs-time curve [AUC] and C_{max}) must fall within a range of 80% to 125%[1]
- Additionally, the manufacturer is allowed to select the sample of the drug to be tested, instead of providing a test sample that has been randomly selected[2]
- While the regulatory criteria for bioequivalence may be applicable for most drugs, they may not address some of the potential problems that can arise with critical-dose drugs, such as cyclosporine[3]

References: 1. Center for Drug Evaluation and Research. *Approved Drug Products With Therapeutic Equivalence Evaluations.* 17th ed. Rockville, Md: US Dept of Health and Human Services, Food and Drug Administration; 1997. **2.** Levy G. The clay feet of bioequivalence testing. *J Pharm Pharmacol.* 1995;47:975-977. **3.** Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit.* 1997;19:375-381.

Notes

Specify NEORAL®
cyclosporine capsules and
oral solution for microemulsion

Slide 3



- Published by the FDA, the "Orange Book" is a listing of drugs that have been evaluated and determined to be pharmaceutically equivalent and bioequivalent[1]
- It contains the FDA's advice to the public, to practitioners, and to the states regarding drug product selection; it is most commonly used to determine whether the FDA deems substitution to be acceptable
- However, professional care and judgment should be exercised in using the "Orange Book"[1]
  - For critical-dose drugs, potential problems may occur when patients who have been stabilized on one product are inadvertently switched to another product without careful monitoring (ie, brand to generic, generic to brand, generic to generic)[2]
- Depending on state law, substitution of "AB" rated generics may occur without the physician's knowledge and/or intervention:
  - In states with "permissive" regulations, substitution is at the discretion of the dispensing pharmacist
  - In states with "mandatory" substitution, the pharmacist is required to substitute an "AB" rated generic—unless the physician specifies brand according to state law (eg, "DAW" or "Brand Medically Necessary")

References: 1. Center for Drug Evaluation and Research. *Approved Drug Products With Therapeutic Equivalence Evaluations.* 17th ed. Rockville, Md: US Dept of Health and Human Services, Food and Drug Administration; 1997. **2.** Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit.* 1997;19:375-381.

Notes

Specify NEORAL®
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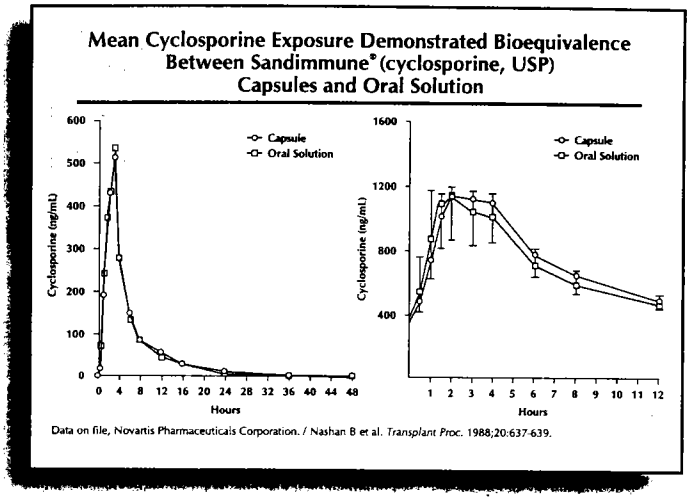
Slide 4



Mean Cyclosporine Exposure Demonstrated Bioequivalence Between Sandimmune® (cyclosporine, USP) Capsules and Oral Solution

- Sandimmune® capsules and oral solution have been shown to be bioequivalent in healthy volunteers and stable renal transplant recipients[1,2]
- However, further investigation of bioequivalence was conducted following isolated reports of nonbioequivalence between the 2 formulations of Sandimmune[3,4]
- While Sandimmune capsules and oral solution both contain the same active ingredient (cyclosporine), the capsule formulation is corn oil–based and the oral solution formulation is olive oil–based

References: 1. Data on file, Novartis Pharmaceuticals Corporation. **2.** Nashan B, Bleck J, Wonigeit K, et al. Effect of the application form of cyclosporine on blood levels: comparison of oral solution and capsules. *Transplant Proc.* 1988;20(suppl 2):637-639. **3.** Schroeder TJ, Shah M, Hariharan S, et al. Increased cyclosporine exposure in patients switched from cyclosporine solution to capsules. Poster presented at: XIIIth International Congress of Nephrology; July 2-6, 1995; Madrid, Spain. Abstract 1684. **4.** Curtis J, Van Buren DH, Pirsch J, et al. Lack of bioequivalence of two Sandimmune® (cyclosporine, USP) formulations in renal transplant patients who absorb cyclosporine poorly. Poster presented at: American Society of Transplant Physicians Meeting; May 9-13, 1998; Chicago, Ill. Abstract 249.

Notes

Specify NEORAL®
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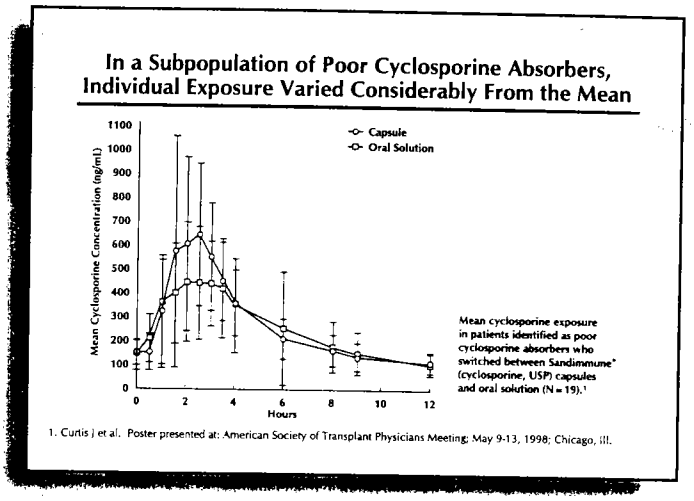
oral solution for microemulsion

Slide 5



In a Subpopulation of Poor Cyclosporine Absorbers, Individual Exposure Varied Considerably From the Mean

- In a preliminary investigation conducted by Curtis et al, the impact of switching between Sandimmune® (cyclosporine, USP) capsules and oral solution was evaluated in a population of 19 maintenance renal transplant recipients identified as poor cyclosporine absorbers*[1,2]
- Findings of this preliminary study suggest that even minor differences in formulation and/or dosage form may result in significant differences in cyclosporine bioavailability in some patient subpopulations (eg, poor cyclosporine absorbers)[2]
  - This study, which is of limited design, is the first that failed to show bioequivalence in patients between the capsule and the oral solution formulations of Sandimmune[2]
- Dose-adjusted mean responses† suggest that cyclosporine bioavailability may be affected in this patient subpopulation[2]
  - Peak concentration (C_{max}) increased 49% ($P<.01$)[2]
  - Exposure (AUC) increased 11% (P=NS)[2]
  - Whole-blood trough level increased 59% (P=NS)[2]
- Individual responses varied considerably[2]

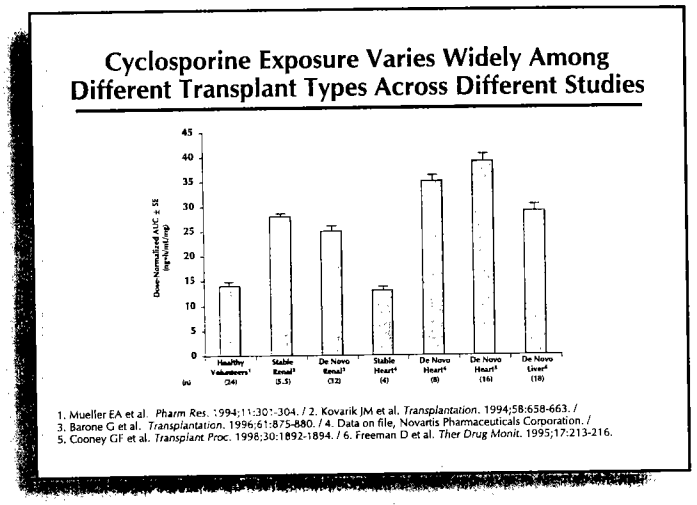
*Maintenance transplant recipients with dose-adjusted $AUC_{0-6} \leq 10$ ng•h/mL per mg (n=19) were defined as poor cyclosporine absorbers according to study protocol.[2]

†Cyclosporine levels determined by radioimmunoassay.

References: 1. Data on file, Novartis Pharmaceuticals Corporation. **2.** Curtis J, Van Buren DH, Pirsch J, et al. Lack of bioequivalence of two Sandimmune® (cyclosporine, USP) formulations in renal transplant patients who absorb cyclosporine poorly. Poster presented at: American Society of Transplant Physicians Meeting; May 9-13, 1998; Chicago, Ill. Abstract 249.

Notes

Slide 7

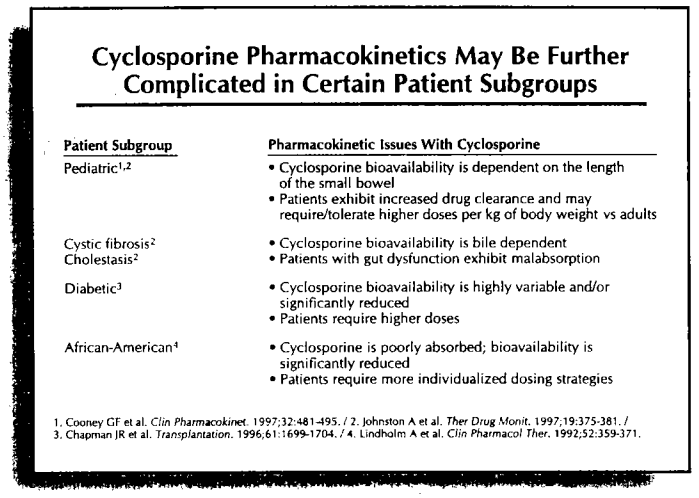


Cyclosporine Exposure Varies Widely Among Different Transplant Types Across Different Studies

- Experience in the development of Neoral® indicates that pharmacokinetic profiles obtained from healthy volunteers are not necessarily predictive of cyclosporine exposure in all subpopulations of transplant recipients
- As this bar graph shows, Neoral provided increased cyclosporine bioavailability that appreciably differed by transplant type[1-6]
- In fact, in de novo heart and liver transplant recipients, cyclosporine exposure was more than doubled vs healthy volunteers, even though the cyclosporine doses were not appreciably different between the groups[1,4-6]
- With critical-dose drugs, such as cyclosporine, unpredictable changes in blood concentrations may result in serious, and sometimes life-threatening, changes in efficacy or toxicity[7,8]

References: 1. Mueller EA, Kovarik JM, van Bree JB, et al. Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. *Pharm Res.* 1994;11:301-304. **2.** Kovarik JM, Mueller EA, van Bree JB, et al. Cyclosporine pharmacokinetics and variability from a microemulsion formulation—a multicenter investigation in kidney transplant patients. *Transplantation.* 1994;58:658-663. **3.** Barone G, Chang CT, Choc MG Jr, et al. The pharmacokinetics of a microemulsion formulation of cyclosporine in primary renal allograft recipients. *Transplantation.* 1996;61:875-880. **4.** Data on file, Novartis Pharmaceuticals Corporation. **5.** Cooney GF, Jeevanandam V, Choudhury S, et al. Comparative bioavailability of Neoral and Sandimmune in cardiac transplant recipients over 1 year. *Transplant Proc.* 1998;30:1892-1894. **6.** Freeman D, Grant D, Levy G, et al. Pharmacokinetics of a new oral formulation of cyclosporine in liver transplant recipients. *Ther Drug Monit.* 1995;17:213-216. **7.** Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit.* 1997;19:375-381. **8.** Freise CE, Galbraith CA, Nikolai BJ, et al. Risks associated with conversion of stable patients after liver transplantation to the microemulsion formulation of cyclosporine. *Transplantation.* 1998;65:995-997.

Slide 8



Cyclosporine Pharmacokinetics May Be Further Complicated in Certain Patient Subgroups

Patient Subgroup	Pharmacokinetic Issues With Cyclosporine
Pediatric[1,2]	• Cyclosporine bioavailability is dependent on the length of the small bowel • Patients exhibit increased drug clearance and may require/tolerate higher doses per kg of body weight vs adults
Cystic fibrosis[2] Cholestasis[2]	• Cyclosporine bioavailability is bile dependent • Patients with gut dysfunction exhibit malabsorption
Diabetic[3]	• Cyclosporine bioavailability is highly variable and/or significantly reduced • Patients require higher doses
African-American[4]	• Cyclosporine is poorly absorbed; bioavailability is significantly reduced • Patients require more individualized dosing strategies

1. Cooney GF et al. *Clin Pharmacokinet.* 1997;32:481-495. / 2. Johnston A et al. *Ther Drug Monit.* 1997;19:375-381. / 3. Chapman JR et al. *Transplantation.* 1996;61:1699-1704. / 4. Lindholm A et al. *Clin Pharmacol Ther.* 1992;52:359-371.

Cyclosporine Pharmacokinetics May Be Further Complicated in Certain Patient Subgroups

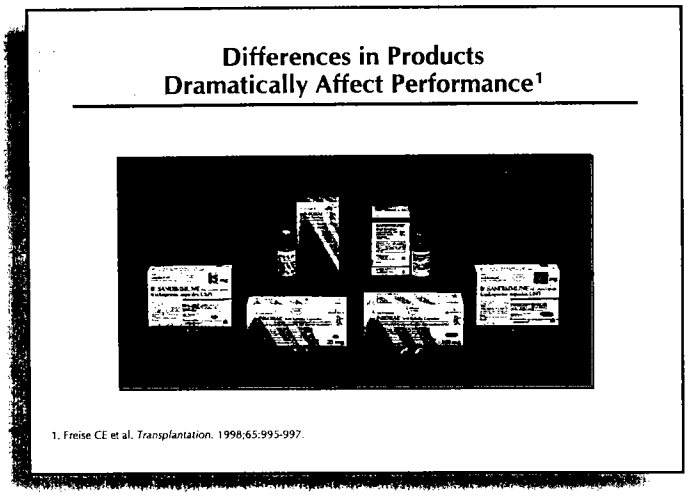
- Certain patient populations are especially prone to poor cyclosporine absorption[1-4]
- Pediatric patients exhibit increased clearance of cyclosporine; as a result, these patients require (and tolerate) higher doses per kilogram of body weight than adults[1,2]
- Among poor absorbers (eg, patients with cystic fibrosis or cholestasis, diabetics, and African-Americans) cyclosporine bioavailability can be highly variable and/or significantly reduced; these patients require higher doses[2-4]
- Experience during the development of Neoral® demonstrated that frequent blood monitoring and dose adjustments, based on individual response, were necessary to maintain each transplant recipient within his or her narrow therapeutic range

References: 1. Cooney GF, Habuck K, Hopp K. Cyclosporin pharmacokinetics in paediatric transplant recipients. *Clin Pharmacokinet.* 1997;32:481-495. **2.** Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit.* 1997;19:375-381. **3.** Chapman JR, O'Connell PJ, Bovington KJ, et al. Reversal of cyclosporine malabsorption in diabetic recipients of simultaneous pancreas and kidney transplants using a microemulsion formulation. *Transplantation.* 1996;61:1699-1704. **4.** Lindholm A, Welsh M, Alton C, et al. Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: racial differences in bioavailability. *Clin Pharmacol Ther.* 1992;52:359-371.

Notes

Specify NEORAL® cyclosporine capsules and oral solution for microemulsion

Slide 9



Differences in Products Dramatically Affect Performance[1]

- Extensively studied, Neoral delivers consistent performance in diverse transplant populations: variability as little as 8%*†
- Due to differences in formulation, Neoral® (cyclosporine for microemulsion) and Sandimmune® (cyclosporine, USP) are not bioequivalent and cannot be used interchangeably without physician supervision
- Any change between these cyclosporine products requires careful blood level monitoring and dosage adjustment, based on individual response, to ensure optimal performance and patient safety[1]
- Specification of cyclosporine product when prescribing, and verification of product when dispensing, helps to ensure consistent exposure of a critical-dose drug, which keeps each patient within his or her narrow therapeutic range

*Data on file, Stable Renal Transplant Recipients, Study OLM102.

†In individual studies of de novo and maintenance renal transplant recipients, the intrasubject variability of the area under the concentration-vs-time curve (AUC), as measured by the percent coefficient of variation (%CV), was 9% to 21%.

Neoral is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. Neoral Soft Gelatin Capsules and Oral Solution are indicated for the prevention of organ rejection in kidney, liver, and heart allogeneic transplant patients. Neoral® (cyclosporine for microemulsion) and Sandimmune® (cyclosporine, USP) are not bioequivalent and cannot be used interchangeably without careful monitoring of cyclosporine blood concentration and dosage adjustments based on individual response. The principal adverse reactions of cyclosporine therapy in transplantation are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. Neoral, a systemic immunosuppressant, may increase the susceptibility to infection and to the development of neoplasia.

Reference: 1. Freise CE, Galbraith CA, Nikolai BJ, et al. Risks associated with conversion of stable patients after liver transplantation to the microemulsion formulation of cyclosporine. *Transplantation*. 1998;65:995-997.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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