CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

Approval Letter
Abbott Laboratories
Pharmaceutical Products Division
Attention: Rebecca Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

Dear Madam:

This is in reference to your abbreviated new drug application dated August 14, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cyclosporine Oral Solution USP (MODIFIED), 100 mg/mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendments dated July 15, December 7, 1999, January 5, and January 21, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cyclosporine Oral Solution USP (MODIFIED), 100 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Neoral Oral Solution, 100 mg/mL, of Novartis Pharmaceuticals Corp.).

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the
proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/

[Signature]

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

3/3/90
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

FINAL PRINTED LABELING
Each mL contains:
cyclosporine, USP 100 mg

Used Dosage: See enclosure for prescribing information.

Store and dispense in glass container. Not compatible with
sterile isotonic fluids. Use aseptically.

Temperature 2°C to 8°C (36°F to 46°F).

(See USP). Do not freeze. Store in refrigerator.

After opened the
contents may be used within 30
months.

Available as 50 mL bottles.

GENGRAF™
cyclosporine oral
solution, USP MODIFIED

NDC 0074-7269-50

FDA APPROVED


Data Source: North Carolina, U.S.A.
GENGRAF™
(cyclosporine oral solution, USP [MODIFIED])
100 mg/mL

Each mL contains:
cyclosporine, USP.......................... 100 mg

Usual Dosage: See enclosure for prescribing information.

WARNING: Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) is NOT BIOEQUIVALENT to Sandimmune® (cyclosporine oral solution, USP [NON-MODIFIED]). Do NOT use interchangeably without a physician’s supervision.

Store and Dispense:
In the original container at controlled room temperature 59°F to 86°F (15°C to 30°C). (See USP). Use contents after opening within 2 months. Do not refrigerate. At temperatures less than 59°F (20°C), a gel may form; slight sediment or flakes may also form. Allow contents to reach room temperature to reverse these effects. There is no impact on product performance or dose.

Trademark
"Sandimmune" is a registered trademark of Novartis Pharmaceuticals Corp.
©Abbott
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

13-1956-2/11

Rx only
**Pediatric Renal Transplantation**

<table>
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<th>Procedure</th>
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<th>ACR (μg/min/m²)</th>
<th>CF (mg/dL)</th>
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**Indications and Usage:**

- **Kidney Transplantation:** Gerstrum™ cyclosporine oral solution USP (MODIFIED) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allograft transplants. Gerstrum™ has been used in combination with prednisone, azathioprine, or cyclosporine.

**Contraindications:**

- Known hypersensitivity to gerstrum™ cyclosporine or related compounds, USP (MODIFIED) should not be used in patients with severe hepatic insufficiency, uncontrolled hypertension, or malnutrition should receive Gerstrum™ cyclosporine oral solution USP (MODIFIED).

**Precautions:**

- Patients with a history of angioedema or urticaria on one or more systemic corticosteroid therapy.

**Adverse Reactions:**

- Hypersensitivity reactions, immunosuppression, and adverse effects of immunosuppressive therapy should be considered when using Gerstrum™ cyclosporine oral solution USP (MODIFIED).

**Dosage and Administration:**

- Administer Gerstrum™ cyclosporine oral solution USP (MODIFIED) as a single dose, preferably in the morning, with food, or within 1 hour of eating.

**General Considerations:**

- Gerstrum™ is available in capsules and oral solution forms. The oral solution is formulated to provide a consistency similar to that of the capsule formulation.

**References:**

- The information presented is based on clinical trials and published literature.

**Notes:**

- For complete prescribing information, please refer to the full prescribing information provided by the manufacturer.
GENGraf™ Oral Solution, USP (MODIFIED)

CLINICAL PHARMACOLOGY: Cyclosporine is a potent immunosuppressant agent that is currently in clinical use for the prevention of organ rejection. It is effective in preventing rejection of kidney, heart, lung, and liver transplants. Cyclosporine acts by inhibiting the transcription of gene expression involved in the development of an immune response.

The plasma concentration of cyclosporine is a good indicator of the drug's effectiveness. However, it can be influenced by factors such as patient compliance, renal function, and drug interactions. Therefore, frequent monitoring of cyclosporine levels is recommended to ensure therapeutic levels are maintained.

PHARMACOKINETICS: Cyclosporine is well absorbed orally and is distributed widely throughout the body. It is metabolized in the liver and eliminated primarily through the kidneys. The half-life of cyclosporine is approximately 4-6 hours, making it necessary to administer the drug frequently.

Adverse Effects: Common adverse effects of cyclosporine include gastrointestinal disturbances, such as nausea, vomiting, and diarrhea. Other adverse effects include hyperkalemia, hypercalcemia, and hypertension. Long-term use of cyclosporine can also lead to immunosuppression, which increases the risk of infections.

Interactions: Cyclosporine can interact with a variety of other drugs, including antibiotics, antacids, and immunosuppressants. Therefore, it is important to inform the healthcare provider of all medications being taken, including over-the-counter drugs and herbal remedies.
Cyclosporine is a potent immunosuppressive agent. Its mechanism of action is complex and involves multiple cellular targets. The primary role of cyclosporine is to inhibit T-cell activation and proliferation, which is achieved through the inhibition of calcineurin, a calcium-dependent phosphatase. Calcineurin inhibition results in the suppression of gene expression, including the production of cytokines and interferon-γ, which are crucial for T-cell-mediated immune responses.

The pharmacokinetics of cyclosporine are complex, with significant variability between individuals. The drug is primarily metabolized in the liver by cytochrome P450 enzymes, and the half-life of the drug ranges from 3 to 10 days, depending on the dose and patient characteristics. The drug's clearance is affected by the presence of inhibitors and inducers of the cytochrome P450 system, including rifampin and erythromycin, respectively.

The effect of cyclosporine on blood pressure is well-documented. Elevated blood pressure is a common side effect, particularly when the drug is used in combination with other antihypertensive medications. The mechanism of this effect is not clear, but it is thought to be related to the inhibition of calcineurin, which can lead to increased vascular smooth muscle cell proliferation and remodeling.


cyclosporine is administered in different dosage forms, including capsules, tablets, and powders. The dosage must be individualized based on the patient's renal function, blood pressure, and other factors. Monitoring of blood pressure and renal function is crucial to ensure that the dosage is appropriate and to prevent the development of side effects.

The use of cyclosporine in pediatric patients is limited, and the appropriate dosage must be carefully titrated based on the patient's weight and renal function. The patient's age, weight, and underlying medical conditions must be considered when determining the dosage.

In conclusion, cyclosporine is a vital immunosuppressive agent, particularly for kidney transplantation. Its effectiveness and safety depend on careful dosing and monitoring, especially in high-risk patients such as children and patients with pre-existing hypertension. The drug's complex pharmacokinetics and interactions with other medications require careful consideration in the treatment of immunosuppression.
**Implementing a Cytoprotective Therapy**

**Parameter**  | **Immunosuppression**
--- | ---
**History**  | 
- Diabetes >50 years old or hypertension
- Proven HLA class II restriction
- Proven, active infection
- Cancer free or nephrologic damage

**Clinical**  | 
- Obese = body weight ≥ 25% body weight
- Proven renal insufficiency
- Anuria or tubular necrosis

**Lab**  | 
- C4 serum trough level ≥ 250 mg/L
- Creatinine in Cr ≤ 2.0 mg/dL
- C4 protein 5% above baseline
- BUN/Cr > 20

**Basics**  | 
- Anemia, elevated creatinine, proteinuria, renal impairment
- Tubular necrosis, acute tubular necrosis, renal dysfunction
- Malignant edema
- Mild focal infiltrates
- Diffuse mesangial fibrosis

**Augmentation**  | 
- Infliximab, etanercept, tocilizumab
- Methotrexate, azathioprine, mycophenolate mofetil
- Ciclosporin, tacrolimus, sirolimus

**Luminal Cecum**  | 
- Tubular atrophy, acute tubular necrosis
- Microscopic hematuria, renal insufficiency,
- corticosteroids, antihypertensives
- Blood pressure control

**Measurement**  | 
- Intracapsular pressure > 40 mm Hg
- Intravascular pressure < 40 mm Hg
- Increase in graft cross sectional area
- AP diameter: 2 Transpl. nephrologist

**Nephraclisis**  | 
- Normal or slightly increased
- Decrease in perfusion
- Decrease in tubular function

**Radiologic Scan**  | 
- Normal or generally decreased
- Decrease in tubular function

**Therapeutically**  | 
- Responds to increased cyclosporine

*p < 0.05, *p < 0.01, **p < 0.001

A form of a cytoprotective-associated nephropathy is characterized by renal deterioration in normal function and morphological changes in the kidneys. From 5% to 15% of transplanted patients who have received cyclosporine therapy may develop a form of cyclosporine nephropathy. The incidence of renal dysfunction is generally low, but it is a common complication of renal transplantation. Although cyclosporine is effective in the treatment of transplant rejection, it can cause significant renal damage. Renal dysfunction is more common in patients who receive higher doses of cyclosporine and in those who have a history of hypertension or diabetes.

In conclusion, the development of cyclosporine-associated nephropathy is a serious concern for transplant recipients. The early identification and management of this complication are crucial to maintain renal function and improve patient outcomes. Further research is needed to understand the mechanisms underlying cyclosporine-induced nephropathy and to develop effective preventive strategies.
Caution should be taken when using cyclosporine with other immunosuppressive drugs. Drug interactions may occur with cyclosporine and other immunosuppressive agents, and nausea, vomiting, diarrhea, and weight gain may occur. Consequently, dosages of other immunosuppressive agents may need to be reduced or even discontinued.

Patients should be informed of the potential risks and benefits of using cyclosporine to treat their disease.

PRECAUTIONS: General: Precautions should be taken in patients with a history of hypertension, diabetes mellitus, congenital heart disease, or valvular heart disease.

PRECAUTIONS: Specific: Precautions should be taken in patients with a history of hepatitis, cirrhosis, or liver disease.

PRECAUTIONS: Special: Precautions should be taken in patients with a history of tuberculosis, salmonellosis, or other infections.

PRECAUTIONS: Pediatric: Precautions should be taken in children with a history of congenital heart disease or valvular heart disease.

PRECAUTIONS: Treatment of Infections: Precautions should be taken in patients with a history of infection or immunosuppression.

PRECAUTIONS: Monitoring: Precautions should be taken in patients with a history of pulmonary hypertension or other cardiac problems.

PRECAUTIONS: Drug Interactions: Precautions should be taken in patients with a history of drug interactions.

PRECAUTIONS: Pregnancy: Precautions should be taken in pregnant women with a history of hypertension.

PRECAUTIONS: Nursing: Precautions should be taken in nursing mothers with a history of hypertension.

PRECAUTIONS: Children: Precautions should be taken in children with a history of congenital heart disease or valvular heart disease.

PRECAUTIONS: Elderly: Precautions should be taken in elderly patients with a history of hypertension or diabetes mellitus.

PRECAUTIONS: Biopsy: Precautions should be taken in patients with a history of biopsy or sampling procedures.

PRECAUTIONS: Laboratory: Precautions should be taken in patients with a history of laboratory tests or examinations.

PRECAUTIONS: Psychological: Precautions should be taken in patients with a history of psychological or psychiatric problems.

PRECAUTIONS: Allergic: Precautions should be taken in patients with a history of allergic reactions.

PRECAUTIONS: Gastrointestinal: Precautions should be taken in patients with a history of gastrointestinal problems.

PRECAUTIONS: Hematologic: Precautions should be taken in patients with a history of hematologic problems.

PRECAUTIONS: Renal: Precautions should be taken in patients with a history of renal problems.

PRECAUTIONS: Ocular: Precautions should be taken in patients with a history of ocular problems.

PRECAUTIONS: Other: Precautions should be taken in patients with a history of other problems.
Cautions and Precautions

Cautions
- Hypertension: Patients with a history of hypertension or chronic kidney disease should be monitored closely.
- Hyponatremia: Patients with hyponatremia should be monitored closely.
- Urinary tract obstruction: Patients with urinary tract obstruction should be monitored closely.
- Allergic reactions: Patients with a history of allergic reactions should be monitored closely.
- Seizure activity: Patients with a history of seizure activity should be monitored closely.

Precautions
- Pregnancy: Patients who are pregnant or planning to become pregnant should be monitored closely.
- Lactation: Patients who are breastfeeding should be monitored closely.
- Children: Patients who are children should be monitored closely.
- Elderly: Patients who are elderly should be monitored closely.

Drug Interactions
- Cimetidine, ranitidine, and famotidine may increase the levels of cyclosporine.
- Sympathomimetic drugs may decrease the levels of cyclosporine.
- Immunosuppressants may decrease the levels of cyclosporine.

Dosing

- Initial dose: The initial dose of cyclosporine should be individualized based on the patient's needs.
- Maintenance dose: The maintenance dose of cyclosporine should be adjusted based on the patient's response.
- Monitoring: The patient's cyclosporine levels should be monitored regularly to ensure therapeutic efficacy.

Adverse Effects

- Hypertension: Patients with hypertension should be monitored closely.
- Hyponatremia: Patients with hyponatremia should be monitored closely.
- Urinary tract obstruction: Patients with urinary tract obstruction should be monitored closely.
- Allergic reactions: Patients with allergic reactions should be monitored closely.
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References

The HIV pressure inhibits (e.g., indinavir, saquinavir, amprenavir) are known to inhibit cyclosporine breakdown, and the concentration of cyclosporine in plasma is increased. Treatment with other drugs can sometimes be associated with increased cyclosporine levels. For example, when patients receiving antiretroviral therapy were treated with indinavir and saquinavir, the mean cyclosporine level increased by 36%. The effect of these interactions is usually transient, and cyclosporine levels return to baseline after discontinuation of the interacting drug.

Other Drug Interactions: Reduced clearance of prednisolone, digoxin, and lamotrigine has been observed when these drugs are administered with cyclosporine. In addition, a decreased elimination of digoxin has been reported after cyclosporine administration. Other drugs may affect the clearance of cyclosporine, and concomitant therapy should be considered when these drugs are used in combination with cyclosporine.

Cyclosporine, by itself, can affect the pharmacokinetics of other drugs. For example, cyclosporine can increase the plasma levels of digoxin, which may necessitate dose adjustments.

Adverse Reactions: The most common adverse reactions associated with the use of cyclosporine are gastrointestinal, dermatological, and immunological. Gastrointestinal reactions include nausea, vomiting, diarrhea, and constipation. Dermatological reactions include rash, hyperpigmentation, and acneiform eruptions. Immunological reactions include allergic reactions, such as urticaria and erythema multiforme.

Cyclosporine is contraindicated in patients with a history of allergy to cyclosporine or any component of the formulation. It is also contraindicated in patients with a history of nephrotoxicity or hepatic toxicity. Pregnant women should be advised of the potential risks associated with the use of cyclosporine during pregnancy.

Cyclosporine is generally well tolerated in pediatric patients, and the safety and efficacy of the drug have been established in clinical trials. However, the long-term effects of cyclosporine on growth, development, and immune function are not fully understood. Therefore, the use of cyclosporine in children should be carefully considered, and the advantages and risks should be discussed with the parents or guardians.

Cyclosporine is a potent immunosuppressant and is used to prevent organ rejection after transplantation. It is also used to treat various autoimmune disorders and to treat certain types of cancer. The drug is available in tablet, capsule, and injectable forms. The tablets are typically administered twice daily, and the capsules and injectable forms are administered once daily.

Cyclosporine is metabolized in the liver and is primarily excreted in the urine. The half-life of cyclosporine is approximately 30-60 hours. Therapy with cyclosporine is usually initiated at a high dose to achieve therapeutic levels, and the dose is then gradually reduced to maintain the desired serum levels. Therapeutic drug monitoring (TDM) is recommended to ensure optimal drug levels.

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**Cardiovascular**
- Hypertension
- Diabetes
- Congestive Heart Failure

**Central Nervous System**
- Tremor
- Confusion
- Hallucinations

**Gastrointestinal**
- Constipation
- Nausea/Vomiting
- Hyperventilation

**Autonomic Nervous System**
- Paresthesia

**Hematopoietic**
- Thrombocytopenia
- Leukopenia

**Respiratory**
- Dyspnea

**Mucocutaneous**
- Rash

**Complications**
- Septicemia
- Arrhythmia
- Systemic fungal infection
- Local fungal infection
- Cytomegalovirus
- Other viral infection

**Corticosteroid Treatment**
- Prednisone

**Antibiotics with Broad Spectrum**
- Cephalosporins

**Sepsis**
- 5%

**Arrhythmia**
- 4%

**Systemic Fungal Infection**
- 3%

**Local Fungal Infection**
- 7.5%

**Cytomegalovirus**
- 4.8%

**Other Viral Infection**
- 15.6%

**Other Tissue Infection**
- 21.3%

**Wound and Skin Infection**
- 7.0%

**Pneumonia**
- 6.2%

**Some patients also received ALC**

**Rhinoviruses:** The principal adverse events associated with the use of cimetidine in asymptomatic patients were respiratory symptoms and allergic reactions (1.4% and 0.3%, respectively).

**Cimetidine** (Sodium Chloride) was associated with a higher incidence of adverse events compared to placebo (2.4% vs. 1.1%).

**Rhinovirus** was isolated in 25% of patients in the placebo group and 28% in the cimetidine group.
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</table>

*Includes persons with 25 mg/daily dose group only. *NCDS = Not Otherwise Specified.
In addition, the following adverse events have been reported in 1% to 5% of the patients treated with the cyclosporine enemas group in a randomized clinical trial.

**Adverse Events Occurring in 1% to 5% of Patients Treated with the Cyclosporine Enemas Group in a Randomized Clinical Trial**

<table>
<thead>
<tr>
<th>Body Area</th>
<th>Preferred Term</th>
<th>Cyclosporine ENEMA</th>
<th>Placebo ENEMA</th>
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<tbody>
<tr>
<td>Infection or Potential Infection</td>
<td>Infection-like Symptoms</td>
<td>26.7%</td>
<td>9.4%</td>
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<td></td>
<td>Upper Respiratory Tract Infections</td>
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<td>1.3%</td>
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<td>Cardiovascular System</td>
<td>Hypertension</td>
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<td>Increased Creatinine</td>
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<td>Renal Failure</td>
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<td>Malabsorption Syndrome</td>
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<td>Body as a Whole - General</td>
<td>Pain</td>
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<td></td>
<td>Metabolic and Nutritional Disorders</td>
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<td>Reproductive System</td>
<td>Menstruation</td>
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<td>Skin and Appendages</td>
<td>Hyperkeratosis</td>
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<td>Respiratory System</td>
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<td>Gastrointestinal System</td>
<td>Abdominal Pain</td>
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<td>Rectal Bleed</td>
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<td></td>
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<td>Anemia</td>
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<td>Hematuria</td>
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<td>Hemoglobin</td>
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<td>Transaminases</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100% due to rounding.*

**Adverse Events Occurring in 0.1% to 1% of Patients Treated with the Cyclosporine Enemas Group in a Randomized Clinical Trial**

<table>
<thead>
<tr>
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<th>Preferred Term</th>
<th>Cyclosporine ENEMA</th>
<th>Placebo ENEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection or Potential Infection</td>
<td>Skin and Appendages</td>
<td>19.4%</td>
<td>7.9%</td>
</tr>
<tr>
<td></td>
<td>Respiratory System</td>
<td>Hyperkeratosis</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal System</td>
<td>Anemia</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemoglobin</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transaminases</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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**Adverse Events Occurring in 0.1% or Less of Patients Treated with the Cyclosporine Enemas Group in a Randomized Clinical Trial**

<table>
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<tbody>
<tr>
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<td>Infection-like Symptoms</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Upper Respiratory Tract Infections</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Hypertension</td>
<td>0.1%</td>
<td>0.0%</td>
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<tr>
<td></td>
<td>Increased Creatinine</td>
<td>0.1%</td>
<td>0.0%</td>
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<tr>
<td></td>
<td>Renal Failure</td>
<td>0.1%</td>
<td>0.0%</td>
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<tr>
<td></td>
<td>Malabsorption Syndrome</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Body as a Whole - General</td>
<td>Pain</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>Metabolic and Nutritional Disorders</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Reproductive System</td>
<td>Menstruation</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>Skin and Appendages</td>
<td>Hyperkeratosis</td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>Respiratory System</td>
<td>Bronchospasm, Cough, Dyspnea, Pneumonia</td>
<td>0.1%</td>
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<td>Abdominal Pain</td>
<td>0.1%</td>
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<td></td>
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<td>Rectal Bleed</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>0.0%</td>
</tr>
</tbody>
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**Adverse Events Occurring in 0.01% or Less of Patients Treated with the Cyclosporine Enemas Group in a Randomized Clinical Trial**

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<td>0.0%</td>
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<td></td>
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<td>0.0%</td>
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<tr>
<td>Cardiovascular System</td>
<td>Hypertension</td>
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<tr>
<td></td>
<td>Increased Creatinine</td>
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<td>Renal Failure</td>
<td>0.0%</td>
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<tr>
<td></td>
<td>Malabsorption Syndrome</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Body as a Whole - General</td>
<td>Pain</td>
<td>0.0%</td>
</tr>
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<td></td>
<td>Metabolic and Nutritional Disorders</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Reproductive System</td>
<td>Menstruation</td>
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</tr>
<tr>
<td></td>
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<td>0.0%</td>
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**Adverse Events Occurring in 0.001% or Less of Patients Treated with the Cyclosporine Enemas Group in a Randomized Clinical Trial**

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<td></td>
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

CHEMISTRY REVIEW(S)
1. CHEMIST'S REVIEW NO. #2

2. ANDA #65-025

3. NAME AND ADDRESS OF APPLICANT
   Abbott Laboratories
   Attention: Rebecca A. Welch
   D-491/AP6B
   100 Abbott Park Road
   Abbott Park, IL 60064-3500
   Phone: 847-937-8971
   Fax: 847-937-8002

4. LEGAL BASIS FOR SUBMISSION
   Reference listed drug: Neoral® Oral Solution for microemulsion by Sandoz (now Novartis Pharmaceuticals) NDA #50716, approved 7/14/95.

Abbott states (page 12) that no exclusivity and no petition apply to this application. See also statement on page 13.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
   Gengraf® Oral Solution

7. NONPROPRIETARY NAME
   Cyclosporine Oral Solution, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
   N/A

9. AMENDMENTS AND OTHER DATES:
   Original application: 8/14/98
   Amendment 10/23/98 for Refuse to File 9/24/98
   FDA acknowledgment: 11/27/98
   Amendment 7/15/99 to N/A letter (MINOR) 6/9/99
   Amendment 12/7/99: Revised labeling

10. PHARMACOLOGICAL CATEGORY
    Immunosuppressive agent for the prophylaxis of organ rejection in allogeneic transplants.

11. Rx or OTC Rx
12. RELATED IND/NDA/DMF(s)
   See under #37 DMF CHECKLIST

13. DOSAGE FORM
   Oral Solution

14. POTENCY 100 mg/mL

15. CHEMICAL NAME AND STRUCTURE

   Cyclosporine USP; C₆₂H₁₁₁N₁₁₃O₁₂; M.W. = 1202.64

   \[ \text{[R[R^*,R^*-(E)]]-Cyclic\{L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-\(\alpha\)-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl\}} \]

   CAS [59865-13-3].

16. RECORDS AND REPORTS  N/A

17. COMMENTS

   The innovator has two formulations of cyclosporine, Neoral® and Sandimmune®, which are not bioequivalent. This application references Neoral® as the reference listed drug. In terms of chemistry, the only difference between Neoral® and Sandimmune® is the formulation. Both products are solutions in bottles when they are marketed. Neoral® contains emulsifiers not present in the Sandimmune® formulation.

   Specifications for SangStat/Lilly's Cyclosporine Oral Solution (#64-195, approved 10/31/98) is attached in CR #1.
Contain Trade Secret,
Commercial/Confidential
Information and are not releasable.

Chemistry Review #2
9/21/99
18. CONCLUSIONS AND RECOMMENDATIONS
   Approval recommended.

19. REVIEWER:
    Maria C. Shih

   DATE COMPLETED:
    9/21/99 (12/17/99)
Contain Trade Secret, Commercial/Confidential Information and are not releasable.
38. Chemistry Comments to be Provided to the Applicant

**ANDA:** 65-025  
**APPLICANT:** Abbott Laboratories

**DRUG PRODUCT:** Cyclosporine Oral Solution, USP (Modified), 100 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following in your response:

1. Safety data relative to use of and have been sent on consult to the Division of Antiinfective Drug Products (HFD-520). Comments, if any, will be forwarded to you when the consult is returned.

2. A satisfactory compliance evaluation of firms referenced in the ANDA is required prior to approval.

Sincerely yours,

\[\text{[Signature]}\]

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number  65-025

BIOEQUIVALENCE REVIEW(S)
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-025

APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, 100 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale K. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-025  APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, 100 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generič Drugs
Center for Drug Evaluation and Research
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #65-025
SPONSOR: Abbott Laboratories
DRUG: Cyclosporine Oral Solution
DOSAGE FORM: Oral Solution
STRENGTHS/(s): 100 mg/mL
TYPE OF STUDY: Single-Dose, Fasting and Non-Fasting
STUDY SITE:
CLINICAL:
ANALYTICAL:

STUDY SUMMARY: The fasting and non-fasting studies are acceptable.

DISSOLUTION: The dissolution testing is not required for this drug product because this is an oral solution.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II
INITIAL: ___________________ DATE 12/29/98

BRANCH CHIEF: Shirinwa Nerurkar, Ph.D, BRANCH: II
INITIAL: ___________________ DATE 1/11/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.
INITIAL: ___________________ DATE 1/28/99

DIRECTOR
OFFICE OF GENERIC DRUGS:
INITIAL: ___________________ DATE ___________________
Cyclosporine Oral Solution, USP
100 mg/mL
ANDA #65-025
Reviewer: Kuldeep R. Dhariwal
File name: 65025S.098

Abbott Laboratories
100 Abbott Park Road
Abbott Park
Illinois 60064-3500
Submission Date:
October 23, 1998

Review of Fasting and Non-Fasting Bioequivalence Studies

The firm has submitted fasting and non-fasting bioequivalence studies comparing its cyclosporine oral solution, 100 mg/mL with Neoral® oral solution for microemulsion, 100 mg/mL (Novartis).

Introduction:

It is a potent immunosuppressive agent. Following oral administration of Neoral®, the T_max ranged from 1.5-2.0 hours. The administration of food decreases AUC and C_max. Neoral® is available as soft gelatin capsules (25 mg, 100 mg) and as oral solution (100 mg/mL). Cyclosporine oral solution is also marketed by Sandoz as Sandimmune® oral solution, 100 mg/mL. Sandimmune® and Neoral® are not bioequivalent.

Bioequivalent Study Under Fasting Conditions:

A. Study Information:

Protocol#: M97-721
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: 

Analytical Site:
Principal Investigator: 
Study Dates:
  Group 1 (Subjects 1-28)
  Period I September 16, 1997
  Period II September 23, 1997
  Group 2 (Subjects 29-56)
  Period I September 19, 1997
  Period II September 26, 1997

Analysis Dates: October 1 to October 29, 1997
Study Design: Randomized, two-way crossover design with a wash-out period of 7 days
Randomization Scheme:
AB: 2, 4, 6, 8, 9, 11, 13, 15, 17, 20, 21, 23, 26, 28, 30, 32, 34, 35, 38, 39, 42, 44, 46, 48, 50, 51, 53, 56
BA: 1, 3, 5, 7, 10, 12, 14, 16, 18, 19, 22, 24, 25, 27, 29, 31, 33, 36, 37, 40, 41, 43, 45, 47, 49, 52, 54, 55

Treatments:
A = Cyclosporine Oral Solution, 3 mL x 100 mg/mL; Abbott; Batch #30-735-AR-05; Batch size: liters;
Manufacture Date: August 19, 1997; Assay: 100.7%
B = Neoral®, 3 mL x 100 mg/mL; Novartis; Batch #203x0498;
Expiry Date: November 1, 1998; Assay: 99.8%

Formulation of Test Product: Table 1
Subjects: 56 subjects (39 males, 17 females) were enrolled according to the criteria specified in the protocol
Housing: From the evening before dosing until after the 48 hour blood draw
Dosing: Subjects were dosed after an overnight fast. Three mL of cyclosporine oral solution were placed in an amber bottle and volume was made up to 45 mL with orange juice. After the subjects consumed this solution, the bottle was rinsed three times each time using 45 mL orange juice. The subjects this way consumed a total of 180 mL orange juice.
Sample Collection: Blood samples (7 mL) were collected at predose (0 h) and at following times after dosing: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36 and 48 hours.

B. Study Results:
1. Clinical:
Drop-outs: Subject #40 was withdrawn after dosing in period I (reference product) due to vasovagal reactions (vomiting, syncope, faintness, dizziness, pallor, nausea, headache etc.). Fifty-five subjects completed the study. Subject #17
Adverse Events:

experienced emesis within 70 minutes of
dosing in both periods but he completed
the study. His samples were analyzed but
not included in statistical analysis.
Some subjects experienced nausea,
headache, vasodilation etc. The events
were comparable on test and reference
drugs. Subject #17 vomited 1 hour after
dosing in period I as well as period II.
Subject #19 vomited 5.47 hours after
dosing in period I (test drug) and #40
vomited 1 minute after dosing in period
I (test drug).

Protocol Deviations:

There were a few sampling time
deviations of less than 5 minutes. Two
samples were drawn 11 and 9 minutes
late. Since the deviations were of less
than 10% of designated times, no
adjustments were made in pharmacokinetic
calculations. Some subjects took
medications during the study.

2. Analytical:

NOT TO BE RELEASED UNDER FOI

Method:

Internal Standard:

Linearity:

Standard curve range
1.00 to 1000 ng/mL
QC Samples
2.70, 270.0, 771.00 ng/mL
Correlation coefficients were greater
than 0.9963.

Regression: 1/(concentration)$^2$, linear

Accuracy:

Standards 98.3-104%
QC samples 94.4-95.8%

Precision:

Standards 1.4-4.2%
QC samples 6.3-7.2%

Reassays:

Following samples were reassayed for
reasons shown against them:
Processing error 8
Pharmacokinetic outlier 6

The firm has provided following pre-study method validation
results:

Linearity:

Standard curve range
1.00 to 1000 ng/mL
QC Samples
2.70, 270, 771 ng/mL
Correlation coefficients were greater than 0.9968.

Accuracy:
Inter-day:
Standards 98.1-103.7%
QC samples 98.0-101.4%
Intra-day:
Standards 98.0-103.5%
QC samples 95.5-102.3%

Precision:
Inter-day:
Standards 0.91-9.3%
QC samples 2.8-8.8%
Intra-day:
Standards 0.48-8.8%
QC samples 1.4-13%

Recovery:
2.70 ng/mL 103.2% (34% CV)
771 ng/mL 79.5% (26% CV)
Internal Standard 92.1% (30% CV)
Note: Extracted as well as unextracted samples have high %CV.

Stability:
a) pre-extraction: stable at room temperature for 24 h before extraction
b) autosampler: stable for 24 h
c) after extraction: stable at 4°C for 139 h
d) freeze-thaw: stable over 3 cycles
e) long-term: stability was compared in samples stored in containers and in presence of two anticoagulants:
Cyclosporine was stable for at least 30 days in tubes containing for 40 days in glass tubes containing and for 75 days in glass tubes containing No differences were observed in the results between samples stored in vs containers and also EDTA vs heparin. The reviewer will therefore extrapolate the results and presume that the study samples which were stored in tubes and is anticoagulant were stable for the maximum storage period of 44 days.
3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 2 and Figure 1
Pharmacokinetic Parameters: Table 2
90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>LAUC&lt;sub&gt;t&lt;/sub&gt;</td>
<td>93.91-99.55%</td>
</tr>
<tr>
<td>LAUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>93.90-99.59%</td>
</tr>
<tr>
<td>LC&lt;sub&gt;max&lt;/sub&gt;</td>
<td>94.97-100.46%</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt;</td>
<td>0.98 (0.78-1.98)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;</td>
<td>0.98 (0.75-2.01)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.98 (0.72-1.35)</td>
</tr>
<tr>
<td>Test</td>
<td>0.95 (0.90-0.98)</td>
</tr>
<tr>
<td>Reference</td>
<td>0.95 (0.90-0.97)</td>
</tr>
</tbody>
</table>

Test/Reference Ratio:

AUC<sub>0-t</sub>/AUC<sub>0-inf</sub> Ratio:

Comments:

1. No subjects with first scheduled post-dose time point as C<sub>max</sub>, and no subjects with first measurable drug concentration as C<sub>max</sub>.
2. NOT TO BE RELEASED UNDER FOI: Majority of subjects (46 out of
Bioavailability of Cyclosporine Oral Solution, 100 mg/mL Under Non-Fasting Conditions:

A. Study Information:

Protocol#: M96-570
IRB Approval: Yes
Consent Form Signed: Yes
Clinical Site: 

Analytical Site: 
Principal Investigator: 

Study Dates:
- Group 3 (Subject 24)
  - Period I October 2, 1997
  - Period II October 9, 1997
  - Period III October 30, 1997
- Group 2 (Subject #5,13,18)
  - Period I October 9, 1997
  - Period II October 23, 1997
  - Period III October 30, 1997
- Group 1 (remaining subjects)
  - Period I October 2, 1997
  - Period II October 9, 1997
  - Period III October 23, 1997

Analysis Dates: October 29 to November 8, 1997
Study Design: Randomized, three-way crossover design with a wash-out period of at least 7 days

Randomization Scheme:  
ABC: 6,9,17,18,21  
BCA: 3,12,23  
ACB: 1,8,15,22  
CBA: 7,14,24  
CAB: 2,10,13,19  
BAC: 4,5,11,16,20

Treatments:

A= Cyclosporine Oral Solution, 3x100 mg/mL; Abbott; Batch #30-735-AR-05; administered after a 10 hour fast  

B= Cyclosporine Oral Solution, 3x100 mg/mL; Abbott; Batch #30-735-AR-05; administered after a standard breakfast  

C= Neoral®, 3x100 mg/mL; Novartis; Batch #203x0498; administered after a standard breakfast  

Lot numbers of drug products administered in this study are the same as those for the fasting study.

Subjects: 24 subjects (10 male, 14 female) were enrolled, according to inclusion/exclusion criteria specified in the protocol

Dosing: Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting about 10 hours. The dose was given with 180 mL of orange juice.  
Treatment A: Subjects were given a single oral dose of the assigned formulation with 180 mL of orange juice after a 10 hour fast.

Sample Collection: Blood samples (5 mL) were collected at predose (0 h) and at following times after dosing: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 9, 10, 12, 15, 18, 24, 30, 36, and 48 hours.

Housing: From the evening before dosing until after the 48 hour blood draw

B. Study Results:

1. Clinical:
Drop-outs: Subject #3 was withdrawn from the study after period II due to pharyngitis.

Adverse Events: Some subjects experienced nausea, headache, vasodilation etc. The events were comparable on test and reference drugs. Some subjects experienced diarrhea. Subject #12 vomited 50 minutes after dosing in period III (test fasting).

Protocol Deviations: There was one sampling time deviation of more than 5 minutes. Some subjects took concurrent medications.

2. Analytical:

Method: 

Internal Standard: 

Linearity: Standard curve range
1.00 to 1000 ng/mL
QC Samples
2.70, 270.0, 771.00 ng/mL
Correlation coefficients were greater than 0.9956.

Regression: 1/(concentration)^2, linear

Accuracy: Standards 98.9-101.6%
QC samples 99.9-102.9%

Precision: Standards 0.8-5.2%
QC samples 2.7-4.8%

Reassays: Twelve samples were reassayed for pharmacokinetic reasons.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 3, Figure 2
Pharmacokinetic Parameters: Table 4
AUC_{0-t}/AUC_{0-inf} Ratios:
Test Fasting 0.95 (0.91-0.97)
Test Non-fasting 0.95 (0.91-0.97)
Ref. Non-fasting 0.95 (0.91-0.97)
Test non-fasting/Ref. non-fasting: AUC_{0-t} 0.99 (0.90-1.05)
AUC_{0-inf} 0.99 (0.69-1.19)
C_{max} 1.04 (0.71-1.46)
Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.

2. No subjects with first scheduled post-dose time point as \( C_{\text{max}} \), and no subjects with first measurable drug concentration as \( C_{\text{max}} \).

3. NOT TO BE RELEASED UNDER FOI: Majority of subjects had

4. Subject #3 was withdrawn after period II without completing test fasting treatment. The data from this subject were included in the analysis because this study mainly compares test and reference products under non-fasting conditions. The data from subject #12 were not omitted from analysis for the same reason though the subject vomited 50 minutes after dosing in period III (test fasting).

5. Ratios of means for AUC0-t, AUC0-inf, and \( C_{\text{max}} \) between test non-fasting and reference non-fasting are within acceptable limits. The non-fasting study is acceptable.

6. There was some confusion about the labeling of sample tubes for subjects 5, 13, and 18. Ratios of means for AUC and \( C_{\text{max}} \) remain within acceptable limits after omitting these subjects.

7. Food decreased AUC and \( C_{\text{max}} \) consistent with the labeling of the reference listed drug.

In Vitro Dissolution Testing:

The drug product is a solution and therefore dissolution testing is not required.

Recommendations:

1. The in vivo bioequivalence study conducted under fasting conditions by Abbott on its cyclosporine oral solution, 100 mg/mL, lot #30-735-AR-05, comparing it to the reference product Neoral® oral solution 100 mg/mL, lot #203x0498 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that Abbott's cyclosporine oral solution 100 mg/mL is bioequivalent to the reference
product, Neoral* oral solution 100 mg/mL manufactured by Novartis.

2. The bioequivalence study conducted under fed conditions by Abbott on its cyclosporine oral solution 100 mg/mL, lot #30-735-AR-05, comparing it to the reference product Neoral* oral solution 100 mg/mL, lot #203x0498 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Abbott's cyclosporine oral solution 100 mg/mL is similar to that of the reference product Neoral* oral solution 100 mg/mL manufactured by Novartis.

3. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalency and the application is acceptable.

/S/ Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

/S/ Date 1/11/99

Concur: /S/ Date 1/28/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>mg/mL</th>
</tr>
</thead>
<tbody>
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<td>Cyclosporine</td>
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</tr>
<tr>
<td>Castor Oil</td>
<td></td>
</tr>
<tr>
<td>Sorbitan Monoooleate</td>
<td></td>
</tr>
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</table>
Table 2
MEAN BLOOD CYCLOSPORINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY, N=54

<table>
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<th>TIME HR</th>
<th>MEAN1</th>
<th>SD1</th>
<th>MEAN2</th>
<th>SD2</th>
<th>RMEAN12</th>
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<td>1.24</td>
<td>1.34</td>
</tr>
<tr>
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<td>876.76</td>
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</tr>
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</tbody>
</table>

UNIT: BLOOD LEVEL=NG/ML TIME=HRS ARITHMETIC MEANS AND RATIOS

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>MEAN1</th>
<th>SD1</th>
<th>MEAN2</th>
<th>SD2</th>
<th>RMEAN12</th>
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</tr>
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<td>0.01</td>
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</table>

UNIT: AUC=NG HR/ML CMAX=NG/ML Tmax=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

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<tr>
<th>PARAMETER</th>
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12
Table 3
MEAN BLOOD CYCLOSPORINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY. N=24

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<tr>
<th>TIME HR</th>
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<th>MEAN2</th>
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<th>SD3</th>
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<td>700.51</td>
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(Continued)

* n=23

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* n=23

UNIT: AUC=NG HR/ML  CMAX=NG/ML  TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

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LSMEANS AND RATIOS

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1= TEST FASTING
2= TEST NON-FASTING
3= REF. NON-FASTING
FIG 1. BLOOD CYCLOSPORINE LEVELS

CYCLOSPORINE ORAL SOLUTION, 100 MG/ML, ANDA #65-025
UNDER FASTING CONDITIONS
DOSE=3 X 100 MG/ML

TIME, HRS

TRT 1=TEST(ABBOTT) 2=REF(NOVARIS)
FIG 2. BLOOD CYCLOSPORINE LEVELS

CYCLOSPORINE ORAL SOLUTION, 100 MG/ML, ANDA #65-025
UNDER FASTING/NONFASTING CONDITIONS
DOSE=3 X 100 MG/ML

1=TEST(FAST)  2=TEST(FED)  3=REF(FED)
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number  65-025

ADMINISTRATIVE DOCUMENTS
ANDA APPROVAL SUMMARY

ANDA #: 65-025  FIRM: Abbott Laboratories
DRUG PRODUCT: Cyclosporine Oral Solution, USP
DOSAGE: Oral Solution  STRENGTH: 100 mg/mL
CAMP STATEMENT/EIR UPDATE STATUS: Acceptable (8/24/99)
BIO STUDY: Acceptable (1/28/99)

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Not requested (USP drug)

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability is the same as those described in the container section.

LABELING: Acceptable (12/16/99)

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): See below

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): An exhibit lot (Lot #30-735-AR-05) of was manufactured in support of the maximum production size. An attempt was made to package an equal amount of both amber glass bottles and TET bottles (1000 each), actually, glass bottles and TET bottles were filled.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See above

Specifications for active ingredient: Under #23A

Specifications for the finished product: Under #28 and #29

CHEMIST: Maria C. Shih  DATE: 9/21/99

SUPERVISOR: R. Adams  DATE: 12/1/99
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-025       Date of Submission: August 14, 1998 and October 23, 1998

Applicant's Name: Abbott Laboratories

Established Name: Cyclosporine Oral Solution USP (MODIFIED), 100 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:
   a. We acknowledge your proposal for a combined package insert for your separate applications for cyclosporine oral solution and capsules. Please note that these applications must be approved at the same time, or further revisions may be necessary prior to approval.
   b. The Nomenclature Committee has found your proposed proprietary name "Gengraf™" acceptable.
   c. Please note that the comments in this review supersede the ones appearing in the Agency's labeling deficiency letter for your application ANDA 65-003 submitted August 14, 1998.
   d. We acknowledge your comments regarding the established name (Cyclosporine oral solution, USP). Although this is the accurate established name for this product, we ask that you distinguish your product from the non-modified formulation by revising your product's established name to read "Cyclosporine Oral Solution, USP (MODIFIED)" throughout your labels and labeling.

2. CONTAINER - 50 mL (Glass & PET bottle)
   a. See general comments, as applicable.
   b. Include "USUAL DOSAGE" prior to the text "See enclosed...".
c. Revise the "Store and dispense" requirement to read "... 68° to 77°F (20° to 25°C). Do not... two months. See package insert for further information."

d. Include the statement "*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation".

3. CARTON
   a. See comments (a), (b) & (d) under CONTAINER.
   b. Revise the storage requirement to read "temperature 68° to 77°F (20° to 25°C). Use...".
   c. We encourage you to increase the prominence of the statement "Do not rinse syringe before use." using bold face and upper case letters.

4. INSERT
   a. GENERAL
      i. See general comments, as applicable.
      ii. Please assure that the requirements of 21 CFR 201.10(g) are met throughout the text. The established name must appear in certain sections in association with the proprietary name. Please revise your labeling accordingly.
      iii. Include your proprietary name "Gengraf™" in place of Neoral® appearing in the reference listed drug labeling where applicable.
      iv. We ask you to include the term "non-modified" when expressing the established name for Sandimmune® to read "cyclosporine, (non-modified)" where Sandimmune® appears in the insert labeling of the reference listed drug. However, please retain the innovator's proprietary name "Sandimmune®" (i.e., Sandimmune® (cyclosporine [non-modified])) where it appears when making comparison to or substitution of your product for Sandimmune®. In addition, add asterisk to read "*Sandimmune®" in order to acknowledge that "*Sandimmune® is a registered trademark of
Novartis Pharmaceuticals Corporation.

v. Due to the difficulty in determining the dosage form of the reference listed drug utilized during clinical studies (oral solution or capsule), we ask that you assure the following wording appears throughout the insert (including the tables):

Where "Neoral®" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "cyclosporine (MODIFIED)".

Likewise, where "Sandimmune®" appears in the innovator's insert labeling without reference to specific dosage form, revise to read "cyclosporine (non-modified)".

vi. It is preferable to use the term "to" rather than a hyphen when expressing a range.

b. BOXED WARNING

i. First box - First sentence:

... transplant recipients should... [rather than "patients"]

ii. Second box

Delete the first sentence.

c. DESCRIPTION

i. We note that the innovator describes their product as forming a microemulsion in an aqueous environment. Please describe in the first paragraph how your drug product is modified in the same condition.

ii. We ask that you include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. You may add the alcohol content on a w/w basis as well, if you prefer. You are referred to section 502(e) of the Act and 21 CFR 201.10(d)(2) for guidance.
iii. We note that you have indicated "other ingredients". Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this product. If you elect not to mention an inactive ingredient because it is a trade secret and decide to retain the phrase "and other ingredients", provide supporting data concerning the "trade secret".

iv. Include the following as the second paragraph in this section.

**NOTE:** The nomenclature "Cyclosporine Oral Suspension for Microemulsion" has been changed throughout the insert to read "Cyclosporine Oral Solution, USP (MODIFIED)".

v. Please include the structural formula, molecular weight, and molecular formula of your drug products.

d. CLINICAL PHARMACOLOGY

i. Pharmacokinetics - Eighth sentence [Gengraf Capsules ... for microemulsion].

Revise to read as follows:

Gengraf™ capsules (cyclosporine capsules, [MODIFIED]) are bioequivalent to Gengraf™ oral solution (cyclosporine oral solution, [MODIFIED]).

ii. Absorption

A) Delete the second sentence "Gengraf is ... for microemulsion)."

B) Second paragraph:

We have determined that kinetics information appearing in the labeling of reference listed drug can be used in the labeling of all generic drug
applications. Please revise to cite studies of the reference listed drug. Also, we note that you have made comparisons regarding kinetics which do not appear in the labeling of the reference listed drug and should be deleted.

e. CLINICAL TRIALS (Rheumatoid Arthritis) - Table:

i. Please assure that the bars representing different regimens are distinguished properly.

ii. Revise to read “columns” at the top of the graph. [spelling]

iii. Replace Neoral with “CsA(MODIFIED)”.

iv. Include the legend to read “1 Cyclosporine (MODIFIED)”.

f. INDICATIONS AND USAGE - Revise the last sentence to read as follows:

Cyclosporine (MODIFIED) has been ... corticosteroids”.

g. WARNINGS

Revise to read “dL” rather than “dl” throughout this section.

h. PRECAUTIONS

i. General

A) Special Monitoring of Rheumatoid Arthritis Patients - Third sentence:

... after an increase of the...

B) Special Monitoring for Psoriasis Patients - Fourth paragraph, fourth sentence:

If at any time the serum... [note “bold face”]
ii. Information for Patients - Second paragraph, first sentence:

... receiving cyclosporine.

iii. Drug Interactions (Drugs That May Potentiate Renal Dysfunction):

"sulidac" rather than "sulindrec".

iv. Pediatric Use - Last sentence:

... treatment in pediatric patients with...

i. ADVERSE REACTIONS

i. Rheumatoid Arthritis - Table:

A) Replace "Cyclosporine for Microemulsion" with "Cyclosporine (MODIFIED)". [2 places]

B) Please rewrite headings of the table on each page when you prepare final print.

ii. Psoriasis

A) Second paragraph, first sentence:

... with U.S. controlled clinical studies...

B) Replace "Cyclosporine for Microemulsion" with "Cyclosporine (MODIFIED)".

j. DOSAGE AND ADMINISTRATION

a. First paragraph:

Delete the first sentence.

b. Include the section headings wherever a reference is made to a subsection in the text throughout this section. [e.g., "(see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption)"]

c. Rheumatoid Arthritis - Second paragraph:

... (See WARNINGS...) [plural]
k. HOW SUPPLIED

a. Gengraf Oral Solution

... 100 mg/mL with dispensing syringe (NDC...).

b. Revise the last statement to read as follows:

*Sandimmune® is registered trademark of Novartis Pharmaceuticals Corporation.

Please revise your labels and labeling, as instructed above, and submit in draft or in final print, if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed innovator's labeling with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

CORRESPONDENCE
July 15, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Attention: Mark Anderson, Project Manager

Re:  ANDA 65-025
Cyclosporine Oral Solution, USP (modified)

MINOR AMENDMENT

Dear Sir:

The sponsor is providing this correspondence to address the deficiencies identified in the letter dated June 9, 1999.

The CMC issues identified as "Chemistry Deficiencies, Item 1-5, are addressed in the following attachments.

The issue regarding the safety of the and s similar to the discussion regarding the Cyclosporine capsule under At that time it was felt the data held in the suppliers DMF was adequate to support the use of the associated inactives. In the case of the Cyclosporine Oral Solution the inactive ingredient, is filed under DMF held by Although there is no DMF for the this inactive is also used in the Cyclosporine capsule formulation in approximately the same concentration (ie. capsule).

Regarding the compliance evaluation of the Abbott Laboratories North Chicago manufacturing site, a follow up meeting was held between the sponsor and the Chicago
July 15, 1999
ANDA 65-025
Page two

District on June 25, 1999 to discuss the audit findings. Based on that meeting and subsequent discussions, it is the sponsor’s belief that a recommendation for approval of the Cyclosporine Oral Solution will be made by the second week of August.

The comments from the Labeling Review Branch have been also been addressed. Four copies of the updated package insert and bottle/carton labels are included in this submission.

If you have any questions regarding this information, please call at the number provided below.

Sincerely,

[Signature]

Rebecca A. Welch
Associate Director
Dept. 491, PPD Regulatory Affairs
100 Abbott Park Rd.
Abbott Park IL 60064-6108
847-937-8971
December 7, 1999

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
Document Control Room, Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Attention: Mr. Mark Anderson.

e:  ANDA 65-025
    Gengraf™ Oral Solution
    (cyclosporine oral solution, USP [MODIFIED])

Labeling Fax Amendment

ur Sir:

The sponsor is providing this amendment to address the deficiencies identified in the letter dated October 21, 1999. The letter included comments on the labeling for ANDA 65-025.

In response to the labeling comments are provided. The FPL for the bottle, carton and insert are provided as references 1, 2 and 3. The review copy has 12 mounted copies of each label. The archival copy includes one copy of each label. In addition, the annotated labeling is provided behind the last tab, "Annotated Labels". In order to perform a side comparison, a copy of the innovator bottle label, carton and insert are included. The notated package insert is provided on a side by side label format, where any changes to innovator text has been reflected in the right hand column. This format has been used because it provides a high quality copy and is easier to review.

The version of the innovator insert (June '97) is also provided for the reviewer, however the quality is poor due to the original package insert being printed in blue and not being provided as an aid to the reviewer and is not expected to be used for the review.
Page 2
ANDA 65-025
December 7, 1999

The Gengraf package insert has been provided on disk in Word '97 and is included in the archival copy. This label has been verified to be an exact copy of the FPL but is in an 81/2 x 11" format. This is being provided as a reviewer aid.

This submission consists of one volume. Two copies (archival and review copies) are being provided to the Office of Generic Drugs.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971
Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to File" letter dated September 24, 1998 and your amendment dated October 23, 1998.

NAME OF DRUG: Cyclosporine Oral Solution USP, 100 mg/mL

DATE OF APPLICATION: August 14, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 26, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
October 23, 1998

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Jerry Phillips
Division of Labeling and Program Support
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: ANDA 65-025
Cyclosporine Oral Solution USP (modified)

Dear Sir:

The sponsor is submitting this amendment under Section 505 (j) of the Federal Food, Drug and Cosmetic Act and CFR 314.96 for Cyclosporine Oral Solution USP, 100 mg/mL. This submission is being made in response to a Refuse to File letter dated September 24, 1998 and signed by Mr. Jerry Phillips, Director, Division of Labeling and Program Support.

The Office of Generic Drugs has refused to file the ANDA for Cyclosporine Oral Solution for the reasons stated in the referenced letter. The sponsor, Abbott Laboratories, is responding to the concerns and amending the application within 30 days from the date of the letter.

If you have any comments regarding this information, please contact me at the number provided below.

Thank you for your attention to this matter.

Sincerely,

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
847-937-8971
Abbott Laboratories
Attention: Rebecca A. Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

SEP 24 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated August 14, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Cyclosporine Oral Solution USP, 100 mg/mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

You have failed to provide data on the active drug substance lot used in the manufacture of your test batch. Please provide this data.

You have failed to provide a letter of authorization from the AADA applicant for the approved bulk antibiotic cyclosporine, which would permit the FDA to refer to the approved application to support the approval of your application for Cyclosporine Oral Solution USP, 100 mg/mL. Please provide this authorization from the applicant of the approved antibiotic application for cyclosporine.

You have failed to provide complete blank master batch records for your proposed production batch. These blank batch records must show the maximum batch size proposed as well as packaging records and labeling reconciliation records.

Your proposed labeling as well as the summary of the container/closure system indicate that your proposed product will be packaged in 2 oz. bottles but page 4540 refers to
2 oz. bottles and 5 mL syringes. Please explain this discrepancy.

The application lacks side-by-side comparisons of the proposed labeling versus the labeling for the reference listed drug with all of the differences annotated and explained. Labeling is defined in the regulations to include both container labels and package insert labeling. Please provide this comparison with all differences annotated and explained as per 21 CFR 314.94(a)(8)(iv).

Your form FDA 356h does not contain an original signature. Please provide a new form with an original signature.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Jeffrey Phillips 9/24/88
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP68-1SW
Abbott Park, Illinois 60064-3500

August 14, 1998

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: Gengraf™
Cyclosporine Oral Solution, USP
ANDA

Original Submission

Dear Madam or Sir:

The sponsor, Abbott Laboratories, submits the following information under the provision of section 505 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94. This information consists of Chemistry, Manufacturing and Controls information and two bioequivalence studies comparing Abbott Gengraf™ (Cyclosporine Oral Solution, USP) to the innovator product, Neoral® Oral Solution.

This submission consists of 15 volumes. A complete set of the volumes has been provided as the archival copy (blue). Sections I-VII are being provided for bioavailability/bioequivalence review (orange). Sections I-V and VII-XXI are being provided for chemistry review (red). In addition, a complete copy of the chemistry, manufacturing and controls sections, Sections I-V and VII-XXI, have been provided as the field copy to the FDA Chicago District Office as required in 21 CFR 314.70 (burgundy).

Two additional copies of the Methods Validation (Section XVI) information are included. Although the product is a USP monograph item, the HPLC test methods have been modified in order to assure the degradants are separated from the Cyclosporine A main peak. Abbott Gengraf™ (Cyclosporine Oral Solution, USP) does meet the USP monograph requirements for Cyclosporine Oral Solution, USP.

A complete list of the available samples is included in section XIX. The actual samples of the drug substance and drug product are not included in this submission, but will be provided upon request.
This application meets the requirements for a categorical exclusion for an environmental assessment, under 21 CFR 25.24 because the formulation will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect.

There are no user fees associated with this application.

As always, should you have any questions regarding this information, please call me at the number provided below.

Rebecca A. Welch
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