**GENGRAF® Capsules** (cyclosporine capsules, USP [MODIFIED])

**Pharmacokinetic Parameters (mean±SD)**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUC(0→t) (ng·hr/mL)</th>
<th>CL/F (mL/min/kg)</th>
<th>Dose/weight (mg/kg)</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo liver transplant (N=9)</td>
<td>182±56</td>
<td>2.0±0.5</td>
<td>284±75</td>
<td>0.6±0.1</td>
<td>0.09±0.03</td>
<td>cyclosporine + aspirin, ketoprofen, piroxicam, or indomethacin.</td>
</tr>
</tbody>
</table>

**Dose/weight (mg/kg)**: Administered at a dose of 5 mg/kg/day for group 1 and 3 mg/kg/day for group 2. **CL/F (mL/min/kg)**: Calculated using the formula: CL/F = (Dose/kg) / (Cmax x AUC(0→t)). **Dose/weight (mg/kg)**: The dose administered was 0.09±0.03 mg/kg for the de novo liver transplant patients.

**Clinical Pharmacology**: Cyclosporine is a potent immunosuppressive agent that in animals prolongs survival of allografts involving skin, kidney, liver, heart, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been shown to protect mammalian myocardium and to a greater extent, microvascular reactions such as allograft rejection, delayed hyperacidity, experimental allografts, macrophthalmia, Freund’s adjuvant arthritis, and graft vs. host disease in a variety of organs.

**Toxicity**: The toxic effects of cyclosporine are similar to other immunosuppressive agents and include renal failure, hypertension, pancreatitis, hyperkalemia, and bone marrow suppression. In the pediatric population, cyclosporine does not cause bone marrow suppression in animal models or humans.

**PRECAUTIONS**: Drug Interactions: See table above for information on drug interactions. **Special Population**: Pediatric: Pharmacokinetic data from pediatric patients administered cyclosporine (MODIFIED) or Sandimmune® are very limited. In 15 transplant patients aged 3-16 years, whole blood levels of cyclosporine were well within the therapeutic range as shown by AUC concentrations.

**PK/PD**: The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear. The relationship between administered dose and exposure is dependent on the patient population, the patient, and the formulation. Elimination of cyclosporine is primarily biliary with only 8% of the dose (parent drug and metabolites) excreted in urine. Neither dialysis nor renal failure alters cyclosporine clearance significantly.

**Drug Interactions**: See table above for information on drug interactions. **Genetic Population**: Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and severely elderly renal patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 30 years) showed no significant difference in the pharmacokinetic parameters.

**CLINICAL TRIALS: Rheumatoid Arthritis**: The effectiveness of cyclosporine in severe rheumatoid arthritis was evaluated in five clinical studies involving a total of 728 cyclosporine treated patients. **Summary**: A summary of the results is presented for the "responders" rates per treatment group, with a responder being defined as a patient who had a 20% improvement in the tender and the worst joint count and a 20% improvement in at least 2 of 4 of investigator global, patient global, disability, and erythrocyte sedimentation rates (ESR) for the Studies 651 and 652. In Study 651 and Study 652, the mean AUCs for blood concentrations of M1, M9 and M4N are about 70%, 21% and 10% respectively. Based on the mean AUCs from stable transplant patients (10 patients administered cyclosporine (MODIFIED) and Sandimmune® in a crossover study), and bile concentration data from de novo liver transplant patients of administered cyclosporine (MODIFIED), Sandimmune® (in the pediatric population), cyclosporine administered as cyclosporine (MODIFIED) or Sandimmune® is administered to the patient having the worst condition (MODIFIED).

**PK/PD**: The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear. The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear.
A form of a cyclosporine-associated nephropathy is characterized by serial deterioration in renal function and morphologic changes in the renal biopsy. From 5% to 15% of transplant recipients experience the development of a form of a cyclosporine-associated nephropathy in rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will show features of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, and arteriolopathy, and a striped form of intestinal fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephropathy requires evidence of morphologic changes and a causative role of cyclosporine.

When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported a possible correlation between the appearance of symptoms and a rise in serum creatinine. In addition, the rise in serum creatinine is usually not accompanied by proteinuria or hematuria.

In the event of severe and unresponsive rejection, when rescue therapy with pulsed steroids and monoclonal antibodies fails to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the dose of cyclosporine. When high doses of cyclosporine were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

The development of other malignancies in those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. Patients taking cyclosporine should be warned that exposure to ultraviolet light exposure should be monitored closely. Some malignancies may be fatal. Transplant patients receiving cyclosporine are at increased risk for serious infection with fatal outcome.

There are no data on the use of Gengraf® therapy with other immunosuppressive agents. Moreover, use of Gengraf® therapy with other immunosuppressive agents may increase the risk of immunosuppression rather than the use of cyclosporine alone. The risk of immunosuppression may be either additive or multiplicative. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Prednisone and other immunosuppressants may be used with caution. Some malignancies may be fatal. Transplant patients receiving cyclosporine are at increased risk for serious infection with fatal outcome.

Exophotophobia has been described both in postmarketing reports and in the literature. Manifestations include impaired visual acuity, visual disturbance, dry eyes, and photophobia. Visual disturbances in individual patients.

Rheumatoid Arthritis: Cyclosporine therapy was not associated with any increase in the incidence of malignant lymphomas. Patients should be thoroughly evaluated before and during Gengraf® therapy for the development of malignancies. Moreover, use of Gengraf® therapy with other immunosuppressive agents may induce an excessive immunosuppression which is known to increase the risk of malignancy.

Psoriasis: See also Boxed Warnings for Psoriasis. Since cyclosporine is a potent immunosuppressive agent with a marked potential for serious side effects, particular attention must be paid to its use in patients with a history of malignancies. Since cyclosporine increases the risk of malignancy, cyclosporine treatment should not be started in patients, who have ever had a malignancy. An increase in serum creatinine and/or tubular function may be seen occasionally in individual patients.

Psoriasis: Cyclosporine therapy was not associated with an increased risk of malignant lymphomas. Patients should be thoroughly evaluated before and during Gengraf® therapy for the development of malignant lymphomas. Moreover, use of Gengraf® therapy with other immunosuppressive agents may induce an excessive immunosuppression which is known to increase the risk of malignancy.
Cyclosporine Concentrations

Patients with treated hypertension, before the initiation of Gengraf® therapy, their medication should be adjusted to control blood pressure readings >140 mmHg. If hypertension persists, the dose of Gengraf® should be further reduced or blood pressure should be controlled with anti-inflammatory therapy during Gengraf® treatment. Note: For increased risk of nephrotoxicity, especially if serum creatinine is not achievable after two dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal anti-inflammatory drug and after initiation of new nonsteroidal anti-inflammatory drug therapy during Gengraf® treatment.

Skin lesions not typical for psoriasis should be biopsied before starting Gengraf®. Patients with malignant or premalignant skin lesions should be treated with Gengraf® only after appropriate treatment of such lesions and if no other treatment option exists. Although malignancies have occurred, it is not known whether patients with malignancy at the time of initiating Gengraf® treatment would have developed these malignancies in the absence of Gengraf® treatment.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions:

- Cyclosporine is an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma concentrations of contractions that are substrates of CYP3A4 or P-glycoprotein.
- Cyclosporine is not an inhibitor of CYP1A2, CYP2D6, and CYP2C19
- Cyclosporine is an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma concentrations of contractions that are substrates of CYP3A4 or P-glycoprotein.

The HV-protein interactions (e.g., indinavir, nefilviren, ritonavir, and saquinavir) are known to inhibit cyclosporine-P450 IV-A isoenzyme and may significantly increase the blood concentrations of cyclosporine; however, these interactions are not available. Care should be exercised when these drugs are administered concurrently.

Dosing for Drugs That Increase Cyclosporine Concentrations

- Antidepressants
- Antineoplastic Agents
- Ivermectin
- Nefazodone
- Amiodarone
- Octreotide
- Lamotrigine

The HIV-protein interactions (e.g., indinavir, nefilviren, ritonavir, and saquinavir) are known to inhibit cyclosporine-P450 IV-A isoenzyme and may significantly increase the blood concentrations of cyclosporine; however, these interactions are not available. Care should be exercised when these drugs are administered concurrently.

Other Drug Interactions:

- Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction is not known. Cyclosporine's metabolism is not affected by rifabutin.
- John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss. Rifampin when used to increase the metabolism of other drugs, may increase the risk of hypoglycemia. In 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with an increase in hepatic swelling, renal tubular dilatation, and increased intrahepatic vesicles.

Drugs That Decrease Cyclosporine Concentrations

- Antihypertensives
- Carbamazepine
- Phenytoin
- Cimetidine

The inhibition of cyclosporine-P450 IV-A isoenzyme and may significantly decrease the blood concentrations of cyclosporine; however, these interactions are not available. Care should be exercised when these drugs are administered concurrently.

Carcinogenicity studies were carried out in male and female Sprague-Dawley rats given cyclosporine at doses of up to 25 mg/kg/day. A significant increase in hepatocellular adenomas in the mid-dose males and hepatocellular carcinomas in both mid-dose males and females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas and hepatocellular carcinomas in the male and female groups, respectively. The hepatocellular carcinomas in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose (6 mg/kg). The hepatocellular carcinomas found in Sprague-Dawley rats and mice are considered to be due to a species-specific response to the drug.

There have been reports of a severe drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss. Rifampin when used to increase the metabolism of other drugs, may increase the risk of hypoglycemia. In 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with an increase in hepatic swelling, renal tubular dilatation, and increased intrahepatic vesicles.
Pre-existing infections may also be aggravated. Fatal outcomes have been reported (see ulcer, thrombocytopenia, tinnitus, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic
pronounced without dose reduction or discontinuation.
creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more renal dysfunction (see Postmarketing Experience, Kidney, Liver and Heart Transplantation:
other Viral Infections

<table>
<thead>
<tr>
<th>System Disorders</th>
<th>No.</th>
<th>Sandimmune® Azathioprine Kidney Heart Liver</th>
<th>Placebo (MODIFIED) Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimentary</td>
<td>15%</td>
<td>21% 24% 17% 15% 17%</td>
<td>21% 21% 15% 13% 15% 15%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>17%</td>
<td>24% 19% 20% 18% 20%</td>
<td>18% 19% 16% 16% 17% 16%</td>
</tr>
<tr>
<td>Skin</td>
<td>15%</td>
<td>21% 22% 17% 19% 17%</td>
<td>17% 17% 14% 14% 15% 13%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>18%</td>
<td>22% 15% 21% 21% 19%</td>
<td>21% 22% 17% 17% 20% 17%</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>17%</td>
<td>21% 22% 17% 19% 17%</td>
<td>17% 17% 14% 14% 15% 13%</td>
</tr>
<tr>
<td>Vascular</td>
<td>18%</td>
<td>22% 15% 21% 21% 19%</td>
<td>21% 22% 17% 17% 20% 17%</td>
</tr>
</tbody>
</table>

Infections Complications in Historical Randomized Studies in Renal Transplant Patients Using Sandimmune®

<table>
<thead>
<tr>
<th>Complication</th>
<th>% of Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septicemia</td>
<td>3.3%</td>
</tr>
<tr>
<td>Abscess</td>
<td>0.5%</td>
</tr>
<tr>
<td>Systemic Pneumonia</td>
<td>0.5%</td>
</tr>
<tr>
<td>Local Pneumonia</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cytophlegyemia</td>
<td>4.4%</td>
</tr>
<tr>
<td>Other Viral Infections</td>
<td>0.5%</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>3.3%</td>
</tr>
<tr>
<td>Wound/Sever Infections</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

* Several patients also received AZA.

Postmarketing Experience, Kidney, Liver and Heart Transplantation: BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Gentamicin, infection in renal transplants, de novo disease and renal dysfunction.

Rheumatoid Arthritis: The principal adverse reactions associated with the use of cyclosporine in rheumatoid arthritis are rash, hyperreflexia, hypertension (see WARNINGS, Kidney, Liver and Heart Transplantation).
Reproductive (Female): breast pain, uterine hemorrhage
Respiratory System: abnormal chest sounds, bronchospasm
Skin: atopy, dermatitis, drug eruption, dry skin, eczema, nail disorder, pruritus, skin disorder, urticaria
Special Senses: abnormal vision, carotid, conjunctivitis, deafness, eye pain, eye paresthesia, tinnitus, vestibular disorder
Urinary System: abnormal urine, hematuria, increased BUN, micturition urgency, nocturia, polyuria, polyuria, pyelonephritis, urination

* NOS = Not Otherwise Specified.

Potasiose: The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, gastrointestinal intolerance, hepatotoxicity, paresthesias, platelet or bleeding disorders, red blood cell disorders, oropharyngeal infections, rhinitis, abnormal vision, cataract, conjunctivitis, deafness, eye pain, taste perversion, tinnitus, vestibular disorder.

The dose of Gengraf® should be titrated individually based on cyclosporine trough concentrations, than 10 mg/kg/day.

When Gengraf® is used for Sorfenine® (cyclosporine) (1:1 dose conversion). The Gengraf® dose should subsequently be adjusted to the pre-correction cyclosporine blood trough concentration. Using the same trough concentration target range for Gengraf® as for Sandimmune® (cyclosporine) results in greater cyclosporine exposure when Gengraf® is administered (see CLINICAL PHARMACOLOGY-Pharmacokinetics, Absorption). Patients with suspected poor absorption of Sandimmune® (cyclosporine) require different dosing strategies (see DOSAGE AND ADMINISTRATION-Transplant Patients, with Poor Absorption of Sandimmune® (cyclosporine), below). In some patients, the increase in blood trough concentration is more pronounced and may be of clinical significance.

Until the blood trough concentration attains the pre-correction value, it is strongly recommended that the transplanted patient should not be discharged from the transplant unit until the trough concentration is measured and the following criteria are met:

1. The trough concentration is within the target range for Gengraf®.
2. The patient has been without any significant clinical abnormalities.
3. The patient has been life-threatening adverse events, such as bleeding, or significant disturbances of homeostasis, such as new-onset hypertension.

While several assays and assay matrices are available, there is a consensus that parent-compound-specific assays have been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustment, and assessment of compliance.

If dose reduction is not effective in controlling abnormalities or if the adverse event or abnormality is severe, Gengraf® should be discontinued. The same initial dose and dosage range should be used if Gengraf® is combined with the recommended dose of methotrexate. Most patients can be treated with Gengraf® doses of 3 mg/kg/day or less when combined with methotrexate doses of up to 15 mg/week (see CLINICAL PHARMACOLOGY-Pharmacokinetics, Absorption). At the time of cyclosporine blood trough concentration should be measured more frequently, at least twice a week ideally, if initial dose exceeds 10 mg/kg/day until the concentration stabilizes within the desired range.

Rheumatic Arthritis: The initial dose of Gengraf® (cyclosporine capsules, USP) (MODIFIED) is 2.5 mg/kg/day.