



**GENGRAF<sup>®</sup>**  
(CYCLOSPORINE  
USP)[MODIFIED]

## Reason to choose **GENGRAF<sup>®</sup>** as your modified cyclosporine

The number of kidney,  
liver, and heart transplants  
continually increases<sup>1</sup>

Many variables complicate  
the choice of an  
immunosuppressant

**Consider GENGRAF** due to its clinical evidence  
and history of dependable use

**Kidney, Liver, and Heart Transplantation:** GENGRAF<sup>®</sup> Capsules (cyclosporine capsules, USP [**MODIFIED**]) and GENGRAF<sup>®</sup> Oral Solution (cyclosporine oral solution, USP [**MODIFIED**]) are indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with azathioprine and corticosteroids.

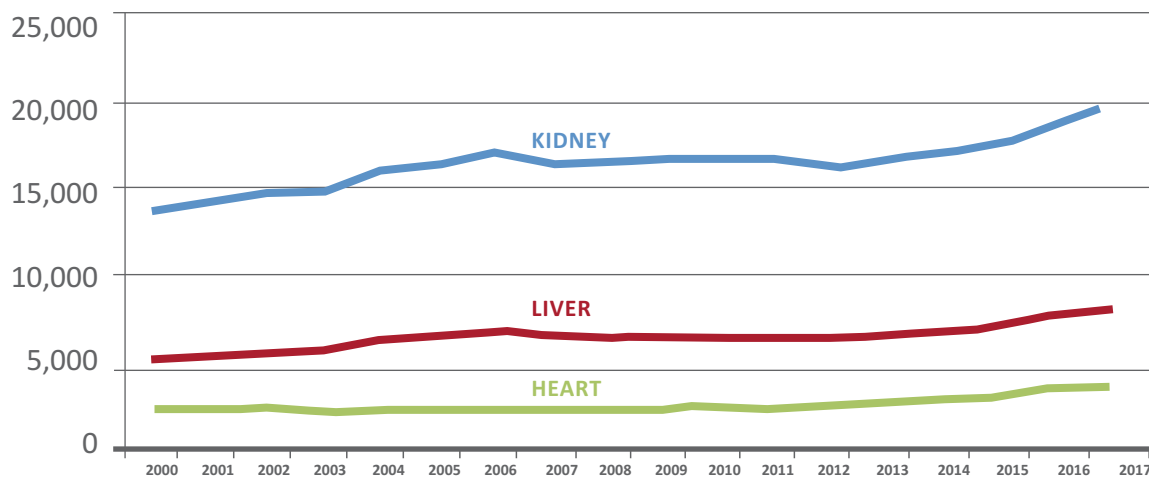
### **SAFETY CONSIDERATIONS<sup>2,3</sup>**

Only physicians experienced in systemic immunosuppressive therapy and management of organ transplant recipients should prescribe GENGRAF. Patients receiving GENGRAF should be managed in facilities with adequate laboratory and supportive medical resources.

## Use of immunosuppressive therapy in kidney, liver, and heart transplantation

**The RATE of kidney, liver, and heart transplants continues to grow yearly<sup>1</sup>**

Total US kidney, liver, and heart transplants, 2000-2017<sup>1</sup>



**46%** increase in  
KIDNEY transplants

**62%** increase in  
LIVER transplants

**48%** increase in  
HEART transplants

## Many variables complicate the choice of immunosuppression regimen

Choosing a suitable immunosuppression regimen is a fairly complex decision due to multiple classes of drugs used in combination regimens.<sup>4</sup> Choice of agents is rooted in protocol. Transplant teams consider a number of recipient-level factors, including a recipient's risk profile, before making final recommendations.

### IMMUNOSUPPRESSANT CONSIDERATIONS

✓ Reason for transplant	✓ Level of social support
✓ Type of transplant	✓ Cost/coverage
✓ Transplant history	✓ Comorbidities
✓ Age & ethnicity	✓ Potential drug interactions
✓ Patient weight	✓ Steroid history
✓ Recipient level of engagement	✓ Likely allergies or side effects

Regimens usually include a calcineurin inhibitor (CNI)—either cyclosporine or tacrolimus—in adjunct with another drug. Cyclosporine is well established as the basis of immunosuppressive therapy following organ transplantation.<sup>5</sup> Regular monitoring of CNI blood levels is required to maintain the therapeutic level of immunosuppressive medications in the blood.

## For your formulary consideration: GENGRAF® (cyclosporine capsules, USP [MODIFIED])

GENGRAF is a generic modified cyclosporine indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with azathioprine and corticosteroids.<sup>2,3</sup>

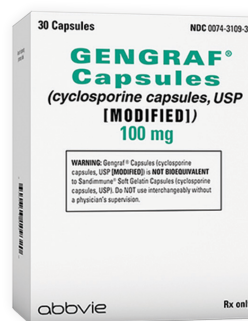
	GENGRAF	NEORAL*	Other Generic Modified Cyclosporines
Registration clinical studies <sup>6-12</sup>	✓	✓	
Safety data	✓ <sup>2,3</sup>	✓ <sup>13</sup>	
AB-rated generic <sup>14</sup>	✓	RLD†	✓
Long-term company reputation	✓	✓	

### Nearly 20 years of trusted clinical experience goes into every dose<sup>6</sup>

- First approved for use in May 2000
- Almost 2 decades of dependable immunosuppressive action



**GENGRAF 25 mg**  
NDC# 0074-3108-32



**GENGRAF 100 mg**  
NDC# 0074-3109-32



**GENGRAF Oral Solution 100 mg/mL**  
NDC# 0074-7269-50

Not shown actual size.

\*NEORAL is a registered trademark of Novartis Pharmaceuticals Corporation.

†Reference Listed Drug

Please see Important Safety Information for GENGRAF on pages 8-10.

Please see accompanying full [Prescribing Information](#) about GENGRAF Capsules.

Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.

## GENGRAF® (cyclosporine capsules, USP [MODIFIED]) clinical trials<sup>7-12, 15</sup>

For a generic medication, GENGRAF has had an abundance of clinical research conducted for therapeutic credibility. In total, 1,909 transplant recipients received GENGRAF capsule in clinical studies.

M97-685 Bioavailability <sup>7</sup>	<ul style="list-style-type: none"><li>• A single-dose, fasting, randomized crossover study</li><li>• To compare the bioavailability of GENGRAF with that of Neoral®</li></ul>
M97-686 Bioavailability <sup>8</sup>	<ul style="list-style-type: none"><li>• A single dose, randomized, three-period crossover study</li><li>• To compare the effect of food on the bioavailability of GENGRAF with that of Neoral</li></ul>
M97-761 9Kidney Conversion Study <sup>9</sup>	<ul style="list-style-type: none"><li>• Multicenter, open-label conversion study</li><li>• In recipients with a history of renal transplantation</li><li>• To determine interchangeability of GENGRAF with Neoral</li></ul>
M97-813 De Novo Kidney Study <sup>10</sup>	<ul style="list-style-type: none"><li>• Six-month, open-label study conducted at 20 US transplant centers</li><li>• In kidney transplant recipients (n=100)</li><li>• Subjects were randomized to GENGRAF or Neoral</li></ul>
M99-033 De Novo Liver Study <sup>11</sup>	<ul style="list-style-type: none"><li>• Phase 3/4 open-label, randomized pharmacokinetic assessment study</li><li>• In liver transplant recipients (N=44)</li><li>• Subjects were randomized to GENGRAF or Neoral</li></ul>
M99-041 European Conversion Study <sup>12</sup>	<ul style="list-style-type: none"><li>• Open-label European conversion study</li><li>• In kidney transplant recipients (N=41)</li><li>• To determine interchangeability of GENGRAF with Neoral</li></ul>
M99-133 PREFER Study <sup>15</sup>	<ul style="list-style-type: none"><li>• Multi-center, randomized, open-label, phase IV study</li><li>• In stable solid-organ transplant recipients (N=1937)</li><li>• To determine capsule preference between GENGRAF and Neoral</li></ul>

## SAFETY CONSIDERATIONS<sup>2,3</sup>

- Patients treated with GENGRAF are at increased risk for developing lymphoma and other malignancies, particularly of the skin. Some malignancies may be fatal.
- Patients treated with GENGRAF have increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections, which may lead to serious, including fatal, outcomes.

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Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.

## GENGRAF® (cyclosporine capsules, USP [MODIFIED]) is a well-established immunosuppressant<sup>2,3</sup>

- Since immunosuppressants reduce the body's ability to fight illness and disease, patients may have increased susceptibility to infections and the development of neoplasia<sup>2,3</sup>
- Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients<sup>2,3</sup>
- Please refer to the Important Safety Information on the adjacent pages for more details about GENGRAF's safety profile

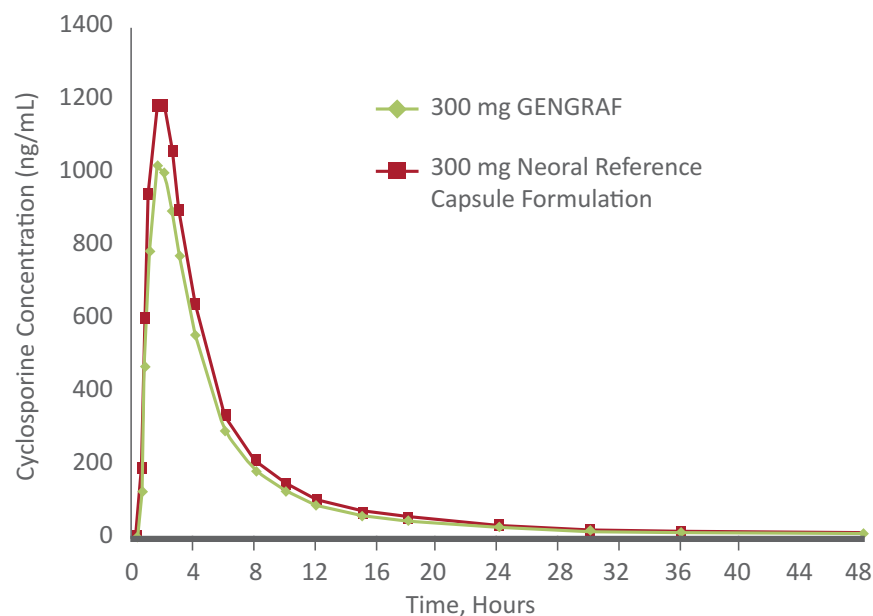
### REMEMBER:

#### Modified cyclosporines are NOT interchangeable with original cyclosporines

- Switching from a cyclosporine to a modified cyclosporine requires extreme caution
- Blood concentrations should be monitored in transplant recipients switching immunosuppression therapy to avoid toxicity due to high concentrations
- Dose adjustments are required to minimize possible organ rejection due to low concentrations

## GENGRAF is AB-rated to Neoral®<sup>7</sup>

### Mean cyclosporine whole blood concentration time profiles of GENGRAF and Neoral<sup>7</sup>



- GENGRAF's pharmacokinetic parameters were comparable to corresponding values obtained after administration of Neoral in stable kidney transplant patients<sup>7</sup>

**Study Design:** An open-label, Phase 1, single-dose, randomized, three-period, and complete-crossover study. Each formulation was administered as a 300-mg dose after a 10-hour fast. The commercially available Neoral cyclosporine 100-mg capsule served as the reference formulation. Sixty-three (63) subjects completed all three periods of the study. The pharmacokinetic parameters of cyclosporine—T<sub>max</sub>, C<sub>max</sub>, the elimination rate constant ( $\beta$ ), half-life ( $t_{1/2}$ ), the area under the blood concentration time curve AUC<sub>0-48</sub>, and the area under the blood concentration-time curve AUC<sub>0-∞</sub>—were calculated. GENGRAF 100-mg hard gelatin capsule formulation was bioequivalent to the Neoral cyclosporine 100-mg capsule formulation since the 90% confidence intervals for AUC<sub>0-∞</sub> and C<sub>max</sub> were within the 0.8–1.25 bioequivalence range and in whole blood level concentrations as illustrated above.

Please see Important Safety Information for GENGRAF on pages 8-10.

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Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.

## Formulary coverage in the modified cyclosporines market<sup>16</sup>

Cyclosporine, USP [MODIFIED] coverage <sup>16</sup>			
	REFERENCE LISTED DRUG	BRANDED GENERIC	GENERIC COVERAGE
Neoral®	●		
<b>GENGRAF®</b> (cyclosporine capsules, USP [MODIFIED])		●	●
Other generics			●

## SAFETY CONSIDERATIONS<sup>2,3</sup>

- Only physicians experienced in systemic immunosuppressive therapy and management of organ transplant recipients should prescribe GENGRAF. Patients receiving GENGRAF should be managed in facilities with adequate laboratory and supportive medical resources.
- Patients treated with GENGRAF are at increased risk for developing lymphoma and other malignancies, particularly of the skin. Some malignancies may be fatal.
- Patients treated with GENGRAF have increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections, which may lead to serious, including fatal, outcomes.
- GENGRAF Capsules and Oral Solution are not bioequivalent to Sandimmune®\* Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP), respectively, and cannot be used interchangeably without physician supervision.
- Cyclosporine blood concentrations should be monitored and dose adjustments made in transplant patients taking GENGRAF to avoid toxicity due to high concentrations and to minimize possible organ rejection due to low concentrations.
- GENGRAF in recommended dosages can cause systemic hypertension and nephrotoxicity.
- Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine; therefore, renal function must be monitored during therapy.
- GENGRAF is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.
- Cases of hepatotoxicity and liver injury, some fatal, have been reported in patients treated with cyclosporine.
- The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

\*Sandimmune is a registered trademark of Novartis Pharmaceuticals Corporation.

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Please see accompanying full [Prescribing Information](#) about GENGRAF Capsules.

Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.

## INDICATION<sup>2,3</sup>

**Kidney, Liver, and Heart Transplantation:** GENGRAF® Capsules (cyclosporine capsules, USP [**MODIFIED**]) and GENGRAF® Oral Solution (cyclosporine oral solution, USP [**MODIFIED**]) are indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine has been used in combination with azathioprine and corticosteroids.

## IMPORTANT SAFETY INFORMATION<sup>2,3</sup>

### WARNING

Only physicians experienced in the management of systemic immunosuppressive therapy for the indicated disease should prescribe GENGRAF. At doses used in solid organ transplantation, only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe GENGRAF. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

GENGRAF, a systemic immunosuppressant, may increase susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients, GENGRAF may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

GENGRAF Capsules (cyclosporine capsules, USP [**MODIFIED**]) and GENGRAF Oral Solution (cyclosporine oral solution, USP [**MODIFIED**]) have increased bioavailability in comparison to Sandimmune®\* Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP), respectively. GENGRAF and Sandimmune are not bioequivalent and cannot be used interchangeably without physician supervision. For a given trough concentration, cyclosporine exposure will be greater with GENGRAF than with Sandimmune. If a patient who is receiving exceptionally high doses of Sandimmune is converted to GENGRAF, particular caution should be exercised. Cyclosporine blood concentrations should be monitored in transplant patients taking GENGRAF to avoid toxicity due to high concentrations. Dose adjustments should be made in transplant patients to minimize possible organ rejection due to low concentrations. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

Cyclosporine, the active ingredient in GENGRAF, in recommended dosages, can cause systemic hypertension and nephrotoxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine; therefore, renal function must be monitored during therapy.

## CONTRAINDICATIONS

GENGRAF is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

## WARNINGS

GENGRAF can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing doses of GENGRAF; therefore, renal and hepatic function must be monitored during therapy. **Due to the potential for additive or synergistic impairment of renal function, caution should be taken when using GENGRAF with other nephrotoxic drugs or other drugs that impair renal function.**

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Please see accompanying full [Prescribing Information](#) about GENGRAF Capsules.

Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.



Patients receiving GENGRAF require frequent monitoring of serum creatinine. Elderly patients should be monitored with particular care, since decreases in renal function occur with age.

**Nephrotoxicity:** GENGRAF can cause nephrotoxicity and hepatotoxicity when used in high doses. It is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

**Thrombotic Microangiopathy:** Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia, which may result in graft failure.

**Hyperkalemia:** Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

**Hepatotoxicity:** Cases of hepatotoxicity and liver injury, including cholestasis, jaundice, hepatitis, and liver failure, have been reported in patients treated with cyclosporine. In some cases, mainly in transplant patients, fatal outcomes have been reported.

**Malignancies:** Patients receiving cyclosporine are at increased risk for the development of lymphomas and other malignancies, particularly those of the skin. Patients taking cyclosporine should be warned to avoid excess exposure to ultraviolet light. Some malignancies may be fatal.

**Serious Infections:** Patients receiving GENGRAF are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes.

**Polyoma Virus Infections:** Patients receiving GENGRAF are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus–associated progressive multifocal leukoencephalopathy (PML) and polyoma virus–associated nephropathy (PVAN), especially due to BK virus infection.

**Neurotoxicity:** There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high-dose methylprednisolone.

Encephalopathy, including posterior reversible encephalopathy syndrome (PRES), has been described both in postmarketing reports and in the literature.

**Special Excipients – Alcohol (Ethanol):** The alcohol content of GENGRAF Capsules should be taken into account when given to patients in whom alcohol intake should be avoided or minimized, e.g., pregnant or breastfeeding women, patients presenting with liver disease or epilepsy, alcoholic patients, or pediatric patients.

## PRECAUTIONS

**Hypertension:** Hypertension is a common side effect of cyclosporine therapy that may persist; antihypertensive therapy may be required. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used.

**Vaccination:** During treatment with cyclosporine, vaccination may be less effective; the use of live attenuated vaccines should be avoided.

**Drug Interactions:** A number of drugs are well substantiated to interact with cyclosporine. In addition, concomitant use of NSAIDs with cyclosporine, particularly in the setting of dehydration, may potentiate renal dysfunction. Caution should be exercised when using other drugs which are known to impair renal function, and close monitoring of renal function (in particular serum creatinine) should be performed.

Please see accompanying full [Prescribing Information](#) about GENGRAF Capsules.

Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.

CYP3A inhibitors may result in increased cyclosporine concentrations, while CYP3A inducers may decrease cyclosporine concentrations. Monitoring of concentrations and appropriate adjustment of GENGRAF dosage should be made as needed with concomitant use of either CYP3A inhibitors or inducers.

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), aliskiren, bosentan, dabigatran, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs.

Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin.

Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. The coadministration of cyclosporine with aliskiren is not recommended. Coadministration of cyclosporine with bosentan or with dabigatran should be avoided. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Cyclosporine may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycemia.

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement St. John's Wort that resulted in subtherapeutic levels of cyclosporine, rejection of transplanted organs, and graft loss. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, and should be avoided.

Please see the full Prescribing Information for a listing of established and other potentially significant drug interactions.

**Pregnancy:** GENGRAF should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus. The alcohol content of GENGRAF Capsules should also be taken into account in pregnant women.

**Nursing Mothers:** Cyclosporine passes into breast milk. Because of the potential for serious adverse drug reactions in nursing infants from GENGRAF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Geriatric Use:** Elderly patients are more likely to develop systolic hypertension on therapy and are more likely to show serum creatinine rises  $\geq 50\%$  above the baseline after 3 to 4 months of therapy. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

## ADVERSE REACTIONS

**Kidney, Liver, and Heart Transplantation:** The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

**Hypertension:** Usually mild to moderate, hypertension may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

**Glomerular Capillary Thrombosis:** Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure.

**Hypomagnesemia:** Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy.

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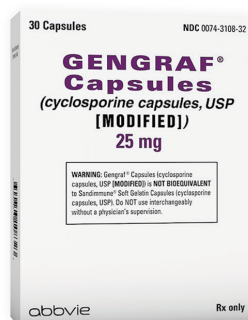
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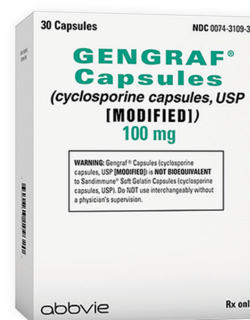
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Fight kidney,  
liver, and heart  
transplant rejection<sup>†</sup>



**GENGRAF 25 mg**  
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**GENGRAF 100 mg**  
NDC# 0074-3109-32



**GENGRAF Oral Solution 100 mg/mL**  
NDC# 0074-7269-50

Not shown actual size.

<sup>†</sup>Indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.

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Please see accompanying full [Prescribing Information](#) about GENGRAF Capsules.

Please see accompanying full [Prescribing Information](#) about GENGRAF Oral Solution.



**GENGRAF 25 mg**  
NDC# 0074-3108-32



**GENGRAF 100 mg**  
NDC# 0074-3109-32



**GENGRAF Oral Solution 100 mg/mL**  
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## SAFETY CONSIDERATIONS<sup>2,3</sup>

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