

AFFORDABLE. DEPENDABLE. FLEXIBLE.

## FIGHT TRANSPLANT REJECTION WITH GENGRAF®

Support your transplant patients\* with nearly  
20 years of reliable immunosuppression



Capsules not actual size

**GENGRAF®**  
(CYCLOSPORINE  
USP) [MODIFIED]

### INDICATION<sup>1</sup>

**Kidney, Liver, and Heart Transplantation:** GENGRAF® Capsules (cyclosporine capsules, USP [MODIFIED]) is 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>1</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 and Sandimmune®† (cyclosporine capsules, USP) Soft Gelatin Capsules are not bioequivalent 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.

\*Indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.

†Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation, which is not affiliated with and does not endorse AbbVie Inc. or its products.

Please [click here](#) for Important Safety Information, including BOXED WARNING.  
Please [click here](#) for full Prescribing Information.

abbvie

AFFORDABLE. DEPENDABLE. FLEXIBLE.

## GENGRAF IS A GENERIC— SO IT'S AFFORDABLE LIKE A GENERIC



### Affordable immunosuppression for transplant patients\*

- Co-pays are less than branded AND generic modified cyclosporines<sup>2</sup>
- 85% of GENGRAF patients' co-pay costs are less than \$20<sup>2</sup>

### Ensure your transplant patients\* get the GENGRAF you prescribe

- 100% of your patients receive GENGRAF when you write DAW<sup>3</sup>
- As you may know, additional blood testing is required when switching modified cyclosporines<sup>4</sup>

### Flexible and dependable dosing options

- Available in 25-mg and 100-mg capsules, and in a 100-mg oral solution
- Dependable immunosuppressive action since 2000

\*Indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.

Please [click here](#) for Important Safety Information, including BOXED WARNING.  
Please [click here](#) for full Prescribing Information.

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

### INDICATION<sup>1</sup>

**Kidney, Liver, and Heart Transplantation:** GENGRAF<sup>®</sup> Capsules (cyclosporine capsules, USP [MODIFIED]) is 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>1</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 and Sandimmune<sup>®†</sup> (cyclosporine capsules, USP) Soft Gelatin Capsules are not bioequivalent 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.

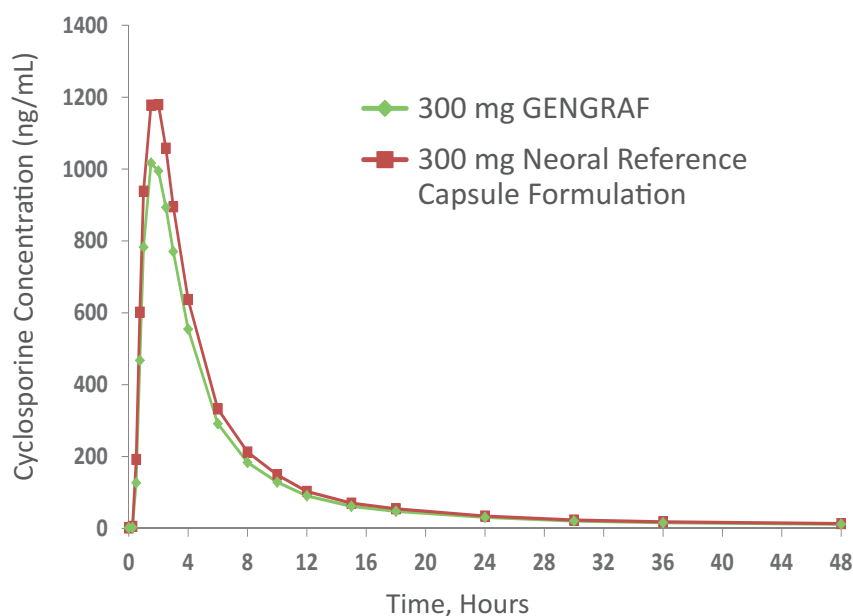
<sup>†</sup>Sandimmune<sup>®</sup> is a registered trademark of Novartis Pharmaceuticals Corporation, which is not affiliated with and does not endorse AbbVie Inc. or its products.

abbvie

AFFORDABLE. DEPENDABLE. FLEXIBLE.

## GENGRAF IS A BRAND— SO IT'S CONSISTENT LIKE A BRAND

### Mean cyclosporine whole blood concentration time profiles of GENGRAF and Neoral®\* – linear scale<sup>5</sup>



\*Neoral® is a registered trademark of Novartis Pharmaceuticals Corporation.

**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 ten-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 –  $T_{max}$ ,  $C_{max}$ , the elimination rate constant ( $\beta$ ), half-life ( $t_{1/2}$ ), the area under the blood concentration-time curve  $AUC_{0-48}$ , and the area under the blood concentration-time curve  $AUC_{0-\infty}$  – 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  $AUC_{0-\infty}$  and  $C_{max}$  were within the 0.8–1.25 bioequivalence range and in whole blood level concentrations as illustrated above.

- GENGRAF Capsules' pharmacokinetic parameters were comparable to corresponding values obtained after administration of Neoral Soft Gelatin Capsules in stable kidney transplant patients<sup>5</sup>
  - Blood concentrations of cyclosporine were similar after administration of GENGRAF or Neoral on all sampling days and at all time points.

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

### INDICATION<sup>1</sup>

**Kidney, Liver, and Heart Transplantation:** GENGRAF<sup>®</sup> Capsules (cyclosporine capsules, USP [MODIFIED]) is 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>1</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 and Sandimmune<sup>®†</sup> (cyclosporine capsules, USP) Soft Gelatin Capsules are not bioequivalent 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.

<sup>†</sup>Sandimmune<sup>®</sup> is a registered trademark of Novartis Pharmaceuticals Corporation, which is not affiliated with and does not endorse AbbVie Inc. or its products.

Please [click here](#) for Important Safety Information, including BOXED WARNING.  
Please [click here](#) for full Prescribing Information.

abbvie

## INDICATION<sup>1</sup>

**Kidney, Liver, and Heart Transplantation:** GENGRAF® Capsules (cyclosporine capsules, USP [MODIFIED]) is 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>1</sup>

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]) has increased bioavailability in comparison to Sandimmune®\* Soft Gelatin Capsules (cyclosporine capsules, USP). 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.**

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.

**References:** 1. GENGRAF [package insert]. North Chicago, IL: AbbVie Inc. 2. Data on file. IMS FIA Dataset (January 2011–December 2015); IMS MM Strategy analysis. 3. Data on file. 2016 DMD Pharmacy Audit. 4. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int.* 2010;77(4): 299–311. 5. Data on file, AbbVie Inc. FDA Submission Bioequivalence Report, #M97-685. Submitted December 19, 1997.

Please [click here](#) for full Prescribing Information.

©2017 AbbVie Inc. North Chicago, IL 60064 031-1913209 July 2017

**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 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.

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 is Pregnancy Category C and should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus. The alcohol content of the GENGRAF formulation 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.

\*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation, which is not affiliated with and does not endorse AbbVie Inc. or its products.



**GENGRAF®**  
(CYCLOSPORINE  
USP) [MODIFIED]

abbvie