# CellCept®
# (mycophenolate mofetil capsules)
# (mycophenolate mofetil tablets)

# CellCept® Oral Suspension
# (mycophenolate mofetil for oral suspension)

# CellCept® Intravenous
# (mycophenolate mofetil hydrochloride for injection)

**Rx only**

**WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS**

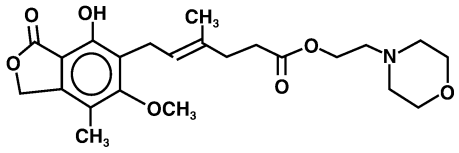
**Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning (see WARNINGS and PRECAUTIONS).**

**Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe CellCept. 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 (see WARNINGS and PRECAUTIONS).**

## DESCRIPTION

CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:




Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 μg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The

pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

CellCept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/mL mycophenolate mofetil.

Inactive ingredients in CellCept 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

Inactive ingredients in CellCept 500 mg tablets include black iron oxide, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc, and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol, and shellac.

Inactive ingredients in CellCept Oral Suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

CellCept Intravenous is the hydrochloride salt of mycophenolate mofetil. The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7$ HCl and a molecular weight of 469.96.

CellCept Intravenous is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of CellCept Intravenous contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the manufacture of CellCept Intravenous to adjust the pH. Reconstitution and dilution with 5% Dextrose Injection USP yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL. (For detailed method of preparation, see **DOSAGE AND ADMINISTRATION**).

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

## Pharmacokinetics

Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 μg/mL).

### Absorption

In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to intravenous mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see **Table 1**).

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA $C_{max}$ was decreased by 40% in the presence of food (see **DOSAGE AND ADMINISTRATION**).

### Distribution

The mean (±SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following intravenous and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed renal graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥460 μg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 μg/mL had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

### Metabolism

Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency (see **CLINICAL PHARMACOLOGY: Special Populations**).

### Excretion

Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as

MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see **OVERDOSAGE**).

Mean (±SD) apparent half-life and plasma clearance of MPA are 17.9 (±6.5) hours and 193 (±48) mL/min following oral administration and 16.6 (±5.8) hours and 177 (±31) mL/min following intravenous administration, respectively.

### Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant Patients

Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac, and hepatic transplant patients. In the early posttransplant period (<40 days posttransplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean $C_{max}$ approximately 32% to 44% lower compared to the late transplant period (3 to 6 months posttransplant).

Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid intravenous CellCept followed by 1.5 g bid oral CellCept resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g CellCept bid.

**Table 1 Pharmacokinetic Parameters for MPA [mean (±SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose), Renal, Cardiac, and Hepatic Transplant Patients (Multiple Doses)**

| | **Dose/Route** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **Total AUC (µg•h/mL)** |
|---|---|---|---|---|
| **Healthy Volunteers (single dose)** | 1 g/oral | 0.80 (±0.36) (n=129) | 24.5 (±9.5) (n=129) | 63.9 (±16.2) (n=117) |
| **Renal Transplant Patients (bid dosing) Time After Transplantation** | **Dose/Route** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **Interdosing Interval AUC(0-12h) (µg•h/mL)** |
| 5 days | 1 g/iv | 1.58 (±0.46) (n=31) | 12.0 (±3.82) (n=31) | 40.8 (±11.4) (n=31) |
| 6 days | 1 g/oral | 1.33 (±1.05) (n=31) | 10.7 (±4.83) (n=31) | 32.9 (±15.0) (n=31) |
| Early (<40 days) | 1 g/oral | 1.31 (±0.76) (n=25) | 8.16 (±4.50) (n=25) | 27.3 (±10.9) (n=25) |
| Early (<40 days) | 1.5 g/oral | 1.21 (±0.81) (n=27) | 13.5 (±8.18) (n=27) | 38.4 (±15.4) (n=27) |
| Late (>3 months) | 1.5 g/oral | 0.90 (±0.24) (n=23) | 24.1 (±12.1) (n=23) | 65.3 (±35.4) (n=23) |
| **Cardiac Transplant Patients (bid dosing) Time After Transplantation** | **Dose/Route** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **Interdosing Interval AUC(0-12h) (µg•h/mL)** |
| Early (Day before discharge) | 1.5 g/oral | 1.8 (±1.3) (n=11) | 11.5 (±6.8) (n=11) | 43.3 (±20.8) (n=9) |
| Late (>6 months) | 1.5 g/oral | 1.1 (±0.7) (n=52) | 20.0 (±9.4) (n=52) | 54.1[a] (±20.4) (n=49) |
| **Hepatic Transplant Patients (bid dosing) Time After Transplantation** | **Dose/Route** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **Interdosing Interval AUC(0-12h) (µg•h/mL)** |
| 4 to 9 days | 1 g/iv | 1.50 (±0.517) (n=22) | 17.0 (±12.7) (n=22) | 34.0 (±17.4) (n=22) |
| Early (5 to 8 days) | 1.5 g/oral | 1.15 (±0.432) (n=20) | 13.1 (±6.76) (n=20) | 29.2 (±11.9) (n=20) |
| Late (>6 months) | 1.5 g/oral | 1.54 (±0.51) (n=6) | 19.3 (±11.7) (n=6) | 49.3 (±14.8) (n=6) |

[a]AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules. Five mL of the 200 mg/mL constituted oral suspension have been shown to be bioequivalent to four 250 mg capsules.

## Special Populations

Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

**Table 2 Pharmacokinetic Parameters for MPA [mean (±SD)] Following Single Doses of Mycophenolate Mofetil Capsules in Chronic Renal and Hepatic Impairment**

| **Renal Impairment (no. of patients)** | **Dose** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **AUC(0-96h) (µg•h/mL)** |
|---|---|---|---|---|
| Healthy Volunteers GFR >80 mL/min/1.73 $m^2$ (n=6) | 1 g | 0.75 (±0.27) | 25.3 (±7.99) | 45.0 (±22.6) |
| Mild Renal Impairment GFR 50 to 80 mL/min/1.73 $m^2$ (n=6) | 1 g | 0.75 (±0.27) | 26.0 (±3.82) | 59.9 (±12.9) |
| Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 $m^2$ (n=6) | 1 g | 0.75 (±0.27) | 19.0 (±13.2) | 52.9 (±25.5) |
| Severe Renal Impairment GFR <25 mL/min/1.73 $m^2$ (n=7) | 1 g | 1.00 (±0.41) | 16.3 (±10.8) | 78.6 (±46.4) |
| **Hepatic Impairment (no. of patients)** | **Dose** | **$T_{max}$ (h)** | **$C_{max}$ (µg/mL)** | **AUC(0-48h) (µg•h/mL)** |
| Healthy Volunteers (n=6) | 1 g | 0.63 (±0.14) | 24.3 (±5.73) | 29.0 (±5.78) |
| Alcoholic Cirrhosis (n=18) | 1 g | 0.85 (±0.58) | 22.4 (±10.1) | 29.8 (±10.7) |

## Renal Insufficiency

In a single-dose study, MMF was administered as capsule or intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 $m^2$] was about 75% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 $m^2$). In addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 $m^2$) was 62.4 µg•h/mL (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see **PRECAUTIONS: Patients with Renal Impairment** and **DOSAGE AND ADMINISTRATION**).

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable to that seen in posttransplant patients without delayed renal graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2-fold to 3-fold higher than in posttransplant patients without delayed renal graft function (see **PRECAUTIONS: Patients with Renal Impairment** and **DOSAGE AND ADMINISTRATION**).

In 8 patients with primary graft non-function following renal transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold.

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 μg/mL), hemodialysis removes only small amounts of MPAG.

### Hepatic Insufficiency

In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g intravenous) study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 μg•h/mL (±15.5).

### Pediatrics

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving CellCept oral suspension at a dose of 600 mg/m$^2$ bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in **Table 3**.

**Table 3 Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Renal Transplantation**

| Age Group | (n) | Time | $T_{max}$ (h) | | Dose Adjusted[a] $C_{max}$ (µg/mL) | | Dose Adjusted[a] $AUC_{0-12}$ (µg•h/mL) | |
|---|---|---|---|---|---|---|---|---|
| | | Early (Day 7) | | | | | | |
| 1 to <2 yr | (6)[d] | | 3.03 | (4.70) | 10.3 | (5.80) | 22.5 | (6.66) |
| 1 to <6 yr | (17) | | 1.63 | (2.85) | 13.2 | (7.16) | 27.4 | (9.54) |
| 6 to <12 yr | (16) | | 0.940 | (0.546) | 13.1 | (6.30) | 33.2 | (12.1) |
| 12 to 18 yr | (21) | | 1.16 | (0.830) | 11.7 | (10.7) | 26.3 | (9.14)[b] |
| | | Late (Month 3) | | | | | | |
| 1 to <2 yr | (4)[d] | | 0.725 | (0.276) | 23.8 | (13.4) | 47.4 | (14.7) |
| 1 to <6 yr | (15) | | 0.989 | (0.511) | 22.7 | (10.1) | 49.7 | (18.2) |
| 6 to <12 yr | (14) | | 1.21 | (0.532) | 27.8 | (14.3) | 61.9 | (19.6) |
| 12 to 18 yr | (17) | | 0.978 | (0.484) | 17.9 | (9.57) | 53.6 | (20.3)[c] |
| | | Late (Month 9) | | | | | | |
| 1 to <2 yr | (4)[d] | | 0.604 | (0.208) | 25.6 | (4.25) | 55.8 | (11.6) |
| 1 to <6 yr | (12) | | 0.869 | (0.479) | 30.4 | (9.16) | 61.0 | (10.7) |
| 6 to <12 yr | (11) | | 1.12 | (0.462) | 29.2 | (12.6) | 66.8 | (21.2) |
| 12 to 18 yr | (14) | | 1.09 | (0.518) | 18.1 | (7.29) | 56.7 | (14.0) |

[a] adjusted to a dose of 600 mg/m$^2$
[b] n=20
[c] n=16
[d] a subset of 1 to <6 yr

The CellCept oral suspension dose of 600 mg/m$^2$ bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45% to 53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1 year to 18 year age range.

### Gender

Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC(0-12h) for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) µg•h/mL while mean (±SD) MPA $C_{max}$ was 9.96 (±6.19) in the males and 10.6 (±5.64) µg/mL in the females. These differences are not of clinical significance.

### Geriatrics

Pharmacokinetics in the elderly have not been studied.

## CLINICAL STUDIES

### Adults

The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients.

## Renal Transplant

*Adults*

The three renal studies compared two dose levels of oral CellCept (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®) and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at 0.05 level) the incidence of treatment failure within the first 6 months following transplantation. **Table 4** and **Table 5** summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving CellCept discontinued without prior biopsy-proven rejection, death or graft loss than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

**Table 4 Renal Transplant Studies Incidence of Treatment Failure (Biopsy-proven Rejection or Early Termination for Any Reason)**

| **USA Study**[a] **(N=499 patients)** | **CellCept 2 g/day (n=167 patients)** | **CellCept 3 g/day (n=166 patients)** | **Azathioprine 1 to 2 mg/kg/day (n=166 patients)** |
|---|---|---|---|
| All treatment failures | 31.1% | 31.3% | 47.6% |
| Early termination without prior acute rejection[b] | 9.6% | 12.7% | 6.0% |
| Biopsy-proven rejection episode on treatment | 19.8% | 17.5% | 38.0% |
| **Europe/Canada/ Australia Study**[c] **(N=503 patients)** | **CellCept 2 g/day (n=173 patients)** | **CellCept 3 g/day (n=164 patients)** | **Azathioprine 100 to 150 mg/day (n=166 patients)** |
| All treatment failures | 38.2% | 34.8% | 50.0% |
| Early termination without prior acute rejection[b] | 13.9% | 15.2% | 10.2% |
| Biopsy-proven rejection episode on treatment | 19.7% | 15.9% | 35.5% |
| **Europe Study**[d] **(N=491 patients)** | **CellCept 2 g/day (n=165 patients)** | **CellCept 3 g/day (n=160 patients)** | **Placebo (n=166 patients)** |
| All treatment failures | 30.3% | 38.8% | 56.0% |
| Early termination without prior acute rejection[b] | 11.5% | 22.5% | 7.2% |
| Biopsy-proven rejection episode on treatment | 17.0% | 13.8% | 46.4% |

[a] Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.
[b] Does not include death and graft loss as reason for early termination.
[c] MMF or azathioprine/cyclosporine/corticosteroids.
[d] MMF or placebo/cyclosporine/corticosteroids.

The cumulative incidence of 12-month graft loss or patient death is presented below. No advantage of CellCept with respect to graft loss or patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients

in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss or patient death at 1 year.

**Table 5 Renal Transplant Studies**
**Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months**

| Study | CellCept 2 g/day | CellCept 3 g/day | Control (Azathioprine or Placebo) |
|---|---|---|---|
| USA | 8.5% | 11.5% | 12.2% |
| Europe/Canada/Australia | 11.7% | 11.0% | 13.6% |
| Europe | 8.5% | 10.0% | 11.5% |

*Pediatrics*

One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m$^2$ bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well tolerated in pediatric patients (see **ADVERSE REACTIONS**), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid CellCept capsules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

## Cardiac Transplant

A double-blind, randomized, comparative, parallel-group, multicenter study in primary cardiac transplant recipients was performed at 20 centers in the United States, 1 in Canada, 5 in Europe and 2 in Australia. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received CellCept 1.5 g bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune® or Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were retransplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

*(1) Rejection:* No difference was established between CellCept and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise.

*(2) Survival:* CellCept was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year (see **Table 6**).

**Table 6 Rejection at 6 Months/Death or Retransplantation at 1 Year**

| | All Patients | | Treated Patients | |
|---|---|---|---|---|
| | **AZA N = 323** | **CellCept N = 327** | **AZA N = 289** | **CellCept N = 289** |
| Biopsy-proven rejection with hemodynamic compromise at 6 months[a] | 121 (38%) | 120 (37%) | 100 (35%) | 92 (32%) |
| Death or retransplantation at 1 year | 49 (15.2%) | 42 (12.8%) | 33 (11.4%) | 18 (6.2%) |

[a] Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥20 mm or a 25% increase; cardiac index <2.0 L/min/$m^2$ or a 25% decrease; ejection fraction ≤30%; pulmonary artery oxygen saturation ≤60% or a 25% decrease; presence of new $S_3$ gallop; fractional shortening was ≤20% or a 25% decrease; inotropic support required to manage the clinical condition.

### Hepatic Transplant

A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565. Per protocol, patients received CellCept 1 g bid intravenously for up to 14 days followed by CellCept 1.5 g bid orally or azathioprine 1 to 2 mg/kg/day intravenously followed by azathioprine 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The actual median oral dose of azathioprine on study was 1.5 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) initially and 1.26 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) at 12 months. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months posttransplantation, one or more episodes of biopsy-proven and treated rejection or death or retransplantation, and (2) the proportion of patients who experienced graft loss (death or retransplantation) during the first 12 months posttransplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death or retransplantation) for 1 year.

#### Results

In combination with corticosteroids and cyclosporine, CellCept obtained a lower rate of acute rejection at 6 months and a similar rate of death or retransplantation at 1 year compared to azathioprine.

**Table 7 Rejection at 6 Months/Death or Retransplantation at 1 Year**

| | AZA N = 287 | CellCept N = 278 |
|---|---|---|
| Biopsy-proven, treated rejection at 6 months (includes death or retransplantation) | 137 (47.7%) | 107 (38.5%) |
| Death or retransplantation at 1 year | 42 (14.6%) | 41 (14.7%) |

## 4BINDICATIONS AND USAGE

### Renal, Cardiac, and Hepatic Transplant

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

## CONTRAINDICATIONS

Allergic reactions to CellCept have been observed; therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. CellCept Intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

## WARNINGS

### (see boxed WARNING)

### Embryofetal Toxicity

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney (see **PRECAUTIONS: Pregnancy).**

### Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. For recommended pregnancy testing and contraception methods (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**

### Lymphoma and Malignancy

Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of

developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE REACTIONS**). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see **ADVERSE REACTIONS**).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see **ADVERSE REACTIONS**).

### Combination with Other Immunosuppressive Agents

CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3), cyclosporine (Sandimmune®, Neoral®) and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

### Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **ADVERSE REACTIONS**).

### Latent Viral Infections

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including CellCept.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BKVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss (see **ADVERSE REACTIONS: Postmarketing Experience**). Patient monitoring may help detect patients at risk for BK virus-associated nephropathy.

Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

### Neutropenia

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu L$] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see **ADVERSE REACTIONS**). Patients receiving CellCept should be monitored for neutropenia (see **PRECAUTIONS: Laboratory Tests**). The development of neutropenia may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **DOSAGE AND ADMINISTRATION**). Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal, cardiac, and hepatic rejection.

Patients receiving CellCept should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

### Pure Red Cell Aplasia (PRCA)

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION.

## PRECAUTIONS

### Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause. Menopause is the permanent end of menstruation and fertility. Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include 1) 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or 2) postsurgical from a bilateral oophorectomy.

### Pregnancy Testing

To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL

immediately before starting CellCept. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient.

In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

### Contraception

Females of reproductive potential taking CellCept must receive contraceptive counseling and use acceptable contraception (see **Table 8** for acceptable contraception methods). Patients must use acceptable birth control during entire CellCept therapy, and for 6 weeks after stopping CellCept, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).

Patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see **PRECAUTIONS: Information for Patients** and **PRECAUTIONS: Drug Interactions: Oral Contraceptives**).

**Table 8 Acceptable Contraception Methods for Females of Reproductive Potential**

**Pick from the following birth control options:**

| | |
|---|---|
| **Option 1**<br><br>**Methods to Use Alone** | • Intrauterine devices (IUDs)<br>• Tubal sterilization<br>• Patient's partner had a vasectomy |

**OR**

| **Option 2** | **Hormone Methods**<br>choose 1 | | **Barrier Methods**<br>choose 1 |
|---|---|---|---|
| **Choose One Hormone Method** *AND* **One Barrier Method** | **Estrogen and Progesterone**<br>• Oral Contraceptive Pill<br>• Transdermal patch<br>• Vaginal ring<br><br>**Progesterone-only**<br>• Injection<br>• Implant | *AND* | • Diaphragm with spermicide<br>• Cervical cap with spermicide<br>• Contraceptive sponge<br>• Male condom<br>• Female condom |

**OR**

| **Option 3** | **Barrier Methods**<br>choose 1 | | **Barrier Methods**<br>choose 1 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Choose One Barrier Method from each column** *(must choose two methods)* | • Diaphragm with spermicide<br>• Cervical cap with spermicide<br>• Contraceptive sponge | *AND* | • Male condom<br>• Female condom |

## Pregnancy Planning

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CellCept should be discussed with the patient.

## Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving CellCept were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active serious digestive system disease.

## Patients with Renal Impairment

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 $m^2$) who have received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of CellCept greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. CellCept may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable, but MPAG AUC(0-12h) was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. In the three controlled studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients

receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

### Infections in Cardiac Transplant Patients

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept (see **ADVERSE REACTIONS**).

There were more herpes virus (H. simplex, H. zoster, and cytomegalovirus) infections in cardiac transplant patients treated with CellCept compared to those treated with azathioprine (see **ADVERSE REACTIONS**).

### Concomitant Medications

It is recommended that CellCept not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept (see **PRECAUTIONS: Drug Interactions**).

### Patients with HGPRT Deficiency

On theoretical grounds, because CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

### Immunizations

During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: Drug Interactions: Live Vaccines**).

### Phenylketonurics

CellCept Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Therefore, care should be taken if CellCept Oral Suspension is administered to patients with phenylketonuria.

### Information for Patients

*See Medication Guide*

- Inform females of reproductive potential that use of CellCept during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, and advise them as to the appropriate steps to manage these risks, including that they must use acceptable contraception (see **WARNINGS: Embryofetal Toxicity, PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**

- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

- Females of reproductive potential must use acceptable birth control during entire CellCept therapy and for 6 weeks after stopping CellCept, unless the patient chooses to avoid heterosexual intercourse completely (abstinence) (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning, Table 8)**.

- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CellCept should be discussed with the patient.

- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.

- Inform patients that they need repeated appropriate laboratory tests while they are taking CellCept.

- Advise patients that they should not breastfeed during CellCept therapy.

### Laboratory Tests

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see **WARNINGS, ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

### Drug Interactions

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. CellCept has not been administered concomitantly with azathioprine.

#### Acyclovir

Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and $C_{max}$. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

#### Antacids With Magnesium and Aluminum Hydroxides

Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox® TC (10 mL qid). The $C_{max}$ and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when

mycophenolate mofetil was administered alone under fasting conditions. CellCept may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that CellCept and the antacid not be administered simultaneously.

### Proton Pump Inhibitors (PPIs)

Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving CellCept has been reported to reduce the exposure to mycophenolic acid (MPA). An approximate reduction of 30 to 70% in the $C_{max}$ and 25% to 35% in the AUC of MPA has been observed, possibly due to a decrease in MPA solubility at an increased gastric pH. The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and CellCept. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with CellCept.

### Cholestyramine

Following single-dose administration of 1.5 g mycophenolate mofetil to 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of CellCept. Therefore, CellCept is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

### Cyclosporine

Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10 stable renal transplant patients. The mean (±SD) AUC(0-12h) and $C_{max}$ of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (±822) ng•h/mL and 753 (±161) ng/mL, respectively, compared to 3245 (±1088) ng•h/mL and 700 (±246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil.

In renal transplant patients, mean MPA exposure ($AUC_{0-12h}$) was approximately 30-50% greater when mycophenolate mofetil is administered without cyclosporine compared with when mycophenolate mofetil is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

### Ganciclovir

Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and $C_{max}$ (n=10) were 54.3 (±19.0) μg•h/mL and 11.5 (±1.8) μg/mL, respectively, after coadministration of the

two drugs, compared to 51.0 (±17.0) μg•h/mL and 10.6 (±2.0) μg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and $C_{max}$ of MPA (n=12) after coadministration were 80.9 (±21.6) μg•h/mL and 27.8 (±13.9) μg/mL, respectively, compared to values of 80.3 (±16.4) μg•h/mL and 30.9 (±11.2) μg/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

### Oral Contraceptives

A study of coadministration of CellCept (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. CellCept may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister CellCept with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).

### Sevelamer

Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA $C_{max}$ and $AUC_{0-12h}$ by 36% and 26% respectively. This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with CellCept. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after CellCept intake to minimize the impact on the absorption of MPA.

### Trimethoprim/sulfamethoxazole

Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered bid, no effect on the bioavailability of MPA was observed. The mean (±SD) AUC and $C_{max}$ of MPA after concomitant administration were 75.2 (±19.8) μg•h/mL and 34.0 (±6.6) μg/mL, respectively, compared to 79.2 (±27.9) μg•h/mL and 34.2 (±10.7) μg/mL, respectively, after administration of mycophenolate mofetil alone.

### Norfloxacin and Metronidazole

Following single-dose administration of mycophenolate mofetil (1 g) to 11 healthy volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole, the mean MPA $AUC_{0-48h}$ was significantly reduced by 33% compared to the

administration of mycophenolate mofetil alone ($p<0.05$). Therefore, CellCept is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA $AUC_{0-48h}$ when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. The mean (±SD) MPA $AUC_{0-48h}$ after coadministration of mycophenolate mofetil with norfloxacin or metronidazole separately was 48.3 (±24) μg·h/mL and 42.7 (±23) μg·h/mL, respectively, compared with 56.2 (±24) μg·h/mL after administration of mycophenolate mofetil alone.

### Ciprofloxacin and Amoxicillin plus Clavulanic Acid

A total of 64 CellCept-treated renal transplant recipients received either oral ciprofloxacin 500 mg bid or amoxicillin plus clavulanic acid 375 mg tid for 7 or at least 14 days. Approximately 50% reductions in median trough MPA concentrations (pre-dose) from baseline (CellCept alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

### Rifampin

In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure ($AUC_{0-12h}$) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, CellCept is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

### Other Interactions

The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

### Live Vaccines

During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: Immunizations**). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see **WARNINGS**).

The genotoxic potential of mycophenolate mofetil was determined in five assays. Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay and the in vivo mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

## Pregnancy

Pregnancy Category D. See **WARNINGS** section.

Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Risks and benefits of CellCept should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using CellCept at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy

Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the healthcare community better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected 1995-2007) on 77 females exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil (MMF) doses equivalent to 0.02 to 0.9 times the recommended human dose for renal and cardiac transplant patients, based on body surface area conversions. In rat offspring, malformations included anophthalmia, agnathia, and hydrocephaly. In rabbit offspring, malformations included ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia.

### Nursing Mothers

Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, 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.

### Pediatric Use

Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of CellCept oral suspension is 600 mg/$m^2$ bid (up to a maximum of 1 g bid). Also see **CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION**.

Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established.

### Geriatric Use

Clinical studies of CellCept did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of

concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see **ADVERSE REACTIONS**).

## ADVERSE REACTIONS

The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections eg, opportunistic infection (see **WARNINGS: Infections** and **WARNINGS: Latent Viral Infections**). The adverse event profile associated with the administration of CellCept Intravenous has been shown to be similar to that observed after administration of oral dosage forms of CellCept.

### CellCept Oral

The incidence of adverse events for CellCept was determined in randomized, comparative, double-blind trials in prevention of rejection in renal (2 active, 1 placebo-controlled trials), cardiac (1 active-controlled trial), and hepatic (1 active-controlled trial) transplant patients.

#### Geriatrics

Elderly patients (≥65 years), particularly those who are receiving CellCept as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus [CMV] tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see **PRECAUTIONS**).

Safety data are summarized below for all active-controlled trials in renal (2 trials), cardiac (1 trial), and hepatic (1 trial) transplant patients. Approximately 53% of the renal patients, 65% of the cardiac patients, and 48% of the hepatic patients have been treated for more than 1 year. Adverse events reported in ≥20% of patients in the CellCept treatment groups are presented below.

867 **Table 9 Adverse Events in Controlled Studies in Prevention of**
868 **Renal, Cardiac or Hepatic Allograft Rejection (Reported in**
869 **≥20% of Patients in the CellCept Group)**

| | Renal Studies | | | Cardiac Study | | Hepatic Study | |
|---|---|---|---|---|---|---|---|
| | **CellCept 2 g/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day** | **CellCept 3 g/day** | **Azathioprine 1.5 to 3 mg/kg/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day** |
| | (n=336) | (n=330) | (n=326) | (n=289) | (n=289) | (n=277) | (n=287) |
| | % | % | % | % | % | % | % |
| **Body as a Whole** | | | | | | | |
| Pain | 33.0 | 31.2 | 32.2 | 75.8 | 74.7 | 74.0 | 77.7 |
| Abdominal pain | 24.7 | 27.6 | 23.0 | 33.9 | 33.2 | 62.5 | 51.2 |
| Fever | 21.4 | 23.3 | 23.3 | 47.4 | 46.4 | 52.3 | 56.1 |
| Headache | 21.1 | 16.1 | 21.2 | 54.3 | 51.9 | 53.8 | 49.1 |
| Infection | 18.2 | 20.9 | 19.9 | 25.6 | 19.4 | 27.1 | 25.1 |
| Sepsis | – | – | – | – | – | 27.4 | 26.5 |
| Asthenia | – | – | – | 43.3 | 36.3 | 35.4 | 33.8 |
| Chest pain | – | – | – | 26.3 | 26.0 | – | – |
| Back pain | – | – | – | 34.6 | 28.4 | 46.6 | 47.4 |
| Ascites | – | – | – | – | – | 24.2 | 22.6 |
| **Hematologic and Lymphatic** | | | | | | | |
| Anemia | 25.6 | 25.8 | 23.6 | 42.9 | 43.9 | 43.0 | 53.0 |
| Leukopenia | 23.2 | 34.5 | 24.8 | 30.4 | 39.1 | 45.8 | 39.0 |
| Thrombocytopenia | – | – | – | 23.5 | 27.0 | 38.3 | 42.2 |
| Hypochromic anemia | – | – | – | 24.6 | 23.5 | – | – |
| Leukocytosis | – | – | – | 40.5 | 35.6 | 22.4 | 21.3 |
| **Urogenital** | | | | | | | |
| Urinary tract infection | 37.2 | 37.0 | 33.7 | – | – | – | – |
| Kidney function abnormal | – | – | – | 21.8 | 26.3 | 25.6 | 28.9 |
| **Cardiovascular** | | | | | | | |
| Hypertension | 32.4 | 28.2 | 32.2 | 77.5 | 72.3 | 62.1 | 59.6 |
| Hypotension | – | – | – | 32.5 | 36.0 | – | – |
| Cardiovascular disorder | – | – | – | 25.6 | 24.2 | – | – |
| Tachycardia | – | – | – | 20.1 | 18.0 | 22.0 | 15.7 |

| | Renal Studies | | | Cardiac Study | | Hepatic Study | |
|---|---|---|---|---|---|---|---|
| | **CellCept 2 g/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day** | **CellCept 3 g/day** | **Azathioprine 1.5 to 3 mg/kg/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day** |
| | (n=336) | (n=330) | (n=326) | (n=289) | (n=289) | (n=277) | (n=287) |
| | % | % | % | % | % | % | % |
| **Metabolic and Nutritional** | | | | | | | |
| Peripheral edema | 28.6 | 27.0 | 28.2 | 64.0 | 53.3 | 48.4 | 47.7 |
| Hyper-cholesteremia | – | – | – | 41.2 | 38.4 | – | – |
| Edema | – | – | – | 26.6 | 25.6 | 28.2 | 28.2 |
| Hypokalemia | – | – | – | 31.8 | 25.6 | 37.2 | 41.1 |
| Hyperkalemia | – | – | – | – | – | 22.0 | 23.7 |
| Hyperglycemia | – | – | – | 46.7 | 52.6 | 43.7 | 48.8 |
| Creatinine increased | – | – | – | 39.4 | 36.0 | – | – |
| BUN increased | – | – | – | 34.6 | 32.5 | – | – |
| Lactic dehydrogenase increased | – | – | – | 23.2 | 17.0 | – | – |
| Hypomagnesemia | – | – | – | – | – | 39.0 | 37.6 |
| Hypocalcemia | – | – | – | – | – | 30.0 | 30.0 |
| **Digestive** | | | | | | | |
| Diarrhea | 31.0 | 36.1 | 20.9 | 45.3 | 34.3 | 51.3 | 49.8 |
| Constipation | 22.9 | 18.5 | 22.4 | 41.2 | 37.7 | 37.9 | 38.3 |
| Nausea | 19.9 | 23.6 | 24.5 | 54.0 | 54.3 | 54.5 | 51.2 |
| Dyspepsia | – | – | – | – | – | 22.4 | 20.9 |
| Vomiting | – | – | – | 33.9 | 28.4 | 32.9 | 33.4 |
| Anorexia | – | – | – | – | – | 25.3 | 17.1 |
| Liver function tests abnormal | – | – | – | – | – | 24.9 | 19.2 |
| **Respiratory** | | | | | | | |
| Infection | 22.0 | 23.9 | 19.6 | 37.0 | 35.3 | – | – |
| Dyspnea | – | – | – | 36.7 | 36.3 | 31.0 | 30.3 |
| Cough increased | – | – | – | 31.1 | 25.6 | – | – |
| Lung disorder | – | – | – | 30.1 | 29.1 | 22.0 | 18.8 |
| Sinusitis | – | – | – | 26.0 | 19.0 | – | – |
| Pleural effusion | – | – | – | – | – | 34.3 | 35.9 |
| **Skin and Appendages** | | | | | | | |
| Rash | – | – | – | 22.1 | 18.0 | – | – |
| **Nervous System** | | | | | | | |
| Tremor | – | – | – | 24.2 | 23.9 | 33.9 | 35.5 |
| Insomnia | – | – | – | 40.8 | 37.7 | 52.3 | 47.0 |
| Dizziness | – | – | – | 28.7 | 27.7 | – | – |
| Anxiety | – | – | – | 28.4 | 23.9 | – | – |
| Paresthesia | – | – | – | 20.8 | 18.0 | – | – |

The placebo-controlled renal transplant study generally showed fewer adverse events occurring in ≥20% of patients. In addition, those that occurred were not only qualitatively similar to the azathioprine-controlled renal transplant studies, but also occurred at lower

rates, particularly for infection, leukopenia, hypertension, diarrhea and respiratory infection.

The above data demonstrate that in three controlled trials for prevention of renal rejection, patients receiving 2 g/day of CellCept had an overall better safety profile than did patients receiving 3 g/day of CellCept.

The above data demonstrate that the types of adverse events observed in multicenter controlled trials in renal, cardiac, and hepatic transplant patients are qualitatively similar except for those that are unique to the specific organ involved.

Sepsis, which was generally CMV viremia, was slightly more common in renal transplant patients treated with CellCept compared to patients treated with azathioprine. The incidence of sepsis was comparable in CellCept and in azathioprine-treated patients in cardiac and hepatic studies.

In the digestive system, diarrhea was increased in renal and cardiac transplant patients receiving CellCept compared to patients receiving azathioprine, but was comparable in hepatic transplant patients treated with CellCept or azathioprine.

Patients receiving CellCept alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **WARNINGS: Lymphoma and Malignancy**). The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥1 year was similar to the incidence reported in the literature for renal allograft recipients.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g daily) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see **WARNINGS: Lymphoma and Malignancy)**. Non-melanoma skin carcinomas occurred in 1.6% to 4.2% of patients, other types of malignancy in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data.

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

Severe neutropenia (ANC $<0.5 \times 10^3/\mu L$) developed in up to 2.0% of renal transplant patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see **WARNINGS: Neutropenia, PRECAUTIONS: Laboratory Tests** and **DOSAGE AND ADMINISTRATION**).

All transplant patients are at increased risk of opportunistic infections. The risk increases with total immunosuppressive load (see **WARNINGS: Infections** and **WARNINGS: Latent Viral Infections**). **Table 10** shows the incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-controlled prevention trials:

**Table 10 Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection**

| | Renal Studies | | | Cardiac Study | | Hepatic Study | |
|---|---|---|---|---|---|---|---|
| | **CellCept 2 g/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day** | **CellCept 3 g/day** | **Azathioprine 1.5 to 3 mg/kg/day** | **CellCept 3 g/day** | **Azathioprine 1 to 2 mg/kg/day** |
| | (n=336) | (n=330) | (n=326) | (n=289) | (n=289) | (n=277) | (n=287) |
| | % | % | % | % | % | % | % |
| Herpes simplex | 16.7 | 20.0 | 19.0 | 20.8 | 14.5 | 10.1 | 5.9 |
| CMV | | | | | | | |
| – Viremia/syndrome | 13.4 | 12.4 | 13.8 | 12.1 | 10.0 | 14.1 | 12.2 |
| – Tissue invasive disease | 8.3 | 11.5 | 6.1 | 11.4 | 8.7 | 5.8 | 8.0 |
| Herpes zoster | 6.0 | 7.6 | 5.8 | 10.7 | 5.9 | 4.3 | 4.9 |
| – Cutaneous disease | 6.0 | 7.3 | 5.5 | 10.0 | 5.5 | 4.3 | 4.9 |
| Candida | 17.0 | 17.3 | 18.1 | 18.7 | 17.6 | 22.4 | 24.4 |
| – Mucocutaneous | 15.5 | 16.4 | 15.3 | 18.0 | 17.3 | 18.4 | 17.4 |

The following other opportunistic infections occurred with an incidence of less than 4% in CellCept patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease; Candida, urinary tract infection, fungemia/disseminated disease, tissue invasive disease; Cryptococcosis; Aspergillus/Mucor; Pneumocystis carinii.

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal studies, with a notably lower incidence of the following: Herpes simplex and CMV tissue-invasive disease.

In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **WARNINGS: Infections**).

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept.

The following adverse events were reported with 3% to <20% incidence in renal, cardiac, and hepatic transplant patients treated with CellCept, in combination with cyclosporine and corticosteroids.

933 **Table 11 Adverse Events Reported in 3% to <20% of Patients Treated**
934 **With CellCept in Combination With Cyclosporine and**
935 **Corticosteroids**

| **Body System** | |
|---|---|
| Body as a Whole | abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis |
| Hematologic and Lymphatic | coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased |
| Urogenital | acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis, nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder |
| Cardiovascular | angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased |
| Metabolic and Nutritional | abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss |
| Digestive | anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis |

| **Body System** | |
|---|---|
| Respiratory | apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, lung edema, lung disorder, neoplasm, pain, pharyngitis, pleural effusion, pneumonia, pneumothorax, respiratory disorder, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration |
| Skin and Appendages | acne, alopecia, fungal dermatitis, hemorrhage, hirsutism, pruritus, rash, skin benign neoplasm, skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, sweating, vesiculobullous rash |
| Nervous | agitation, anxiety, confusion, convulsion, delirium, depression, dry mouth, emotional lability, hallucinations, hypertonia, hypesthesia, nervousness, neuropathy, paresthesia, psychosis, somnolence, thinking abnormal, vertigo |
| Endocrine | Cushing's syndrome, diabetes mellitus, hypothyroidism, parathyroid disorder |
| Musculoskeletal | arthralgia, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis |
| Special Senses | abnormal vision, amblyopia, cataract (not specified), conjunctivitis, deafness, ear disorder, ear pain, eye hemorrhage, tinnitus, lacrimation disorder |

### Pediatrics

The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m$^2$ bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with CellCept capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, leukopenia, and anemia, which were observed in a higher proportion in pediatric patients.

### CellCept Intravenous

The adverse event profile of CellCept Intravenous was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of intravenous and oral CellCept in renal transplant patients in the immediate posttransplant period (administered for the first 5 days). The potential venous irritation of CellCept Intravenous was evaluated by comparing the adverse events attributable to peripheral venous infusion of CellCept Intravenous with those observed in the intravenous placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept Intravenous.

In the active controlled study in hepatic transplant patients, 2 g/day of CellCept Intravenous were administered in the immediate posttransplant period (up to 14 days). The safety profile of intravenous CellCept was similar to that of intravenous azathioprine.

## Postmarketing Experience

*Congenital Disorders: Embryofetal Toxicity:* Congenital malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to mycophenolate mofetil during pregnancy (see **PRECAUTIONS: Pregnancy**).

*Digestive:* Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

*Hematologic and Lymphatic:* Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents.

*Infections:* Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function. BK virus-associated nephropathy has been observed in patients receiving immunosuppressants, including CellCept. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss.

*Respiratory:* Interstitial lung disorders, including fatal pulmonary fibrosis, have been reported rarely and should be considered in the differential diagnosis of pulmonary symptoms ranging from dyspnea to respiratory failure in posttransplant patients receiving CellCept.

## OVERDOSAGE

The experience with overdose of CellCept in humans is very limited. The events received from reports of overdose fall within the known safety profile of the drug. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients and approximately 7 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In adult rats, deaths occurred after single-oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents approximately 3 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

## DOSAGE AND ADMINISTRATION

### Renal Transplantation

#### Adults

A dose of 1 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g/day of CellCept.

#### Pediatrics (3 months to 18 years of age)

The recommended dose of CellCept oral suspension is 600 mg/$m^2$ administered twice daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body surface area of 1.25 $m^2$ to 1.5 $m^2$ may be dosed with CellCept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 $m^2$ may be dosed with CellCept capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

### Cardiac Transplantation

#### Adults

A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients.

### Hepatic Transplantation

#### Adults

A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients.

### CellCept Capsules, Tablets, and Oral Suspension

The initial oral dose of CellCept should be given as soon as possible following renal, cardiac or hepatic transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA $C_{max}$ by 40%. Therefore, it is recommended that CellCept be administered on an empty stomach. However, in stable renal transplant patients, CellCept may be administered with food if necessary.

Patients should be instructed to take a missed dose as soon as they remember, except if it is near the next scheduled dose, and then continue to take CellCept at the usual times.

*Note:*
If required, CellCept Oral Suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

### Patients With Hepatic Impairment

No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

### Geriatrics

The recommended oral dose of 1 g bid for renal transplant patients, 1.5 g bid for cardiac transplant patients, and 1 g bid administered intravenously or 1.5 g bid administered orally in hepatic transplant patients is appropriate for elderly patients (see **PRECAUTIONS: Geriatric Use**).

## Preparation of Oral Suspension

It is recommended that CellCept Oral Suspension be constituted by the pharmacist prior to dispensing to the patient.

CellCept Oral Suspension should not be mixed with any other medication.

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. There are no adequate and well-controlled studies in pregnant women (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS,** and **HANDLING AND DISPOSAL**). Care should be taken to avoid inhalation or direct contact with skin or mucous membranes of the dry powder or the constituted suspension. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water.

1. Tap the closed bottle several times to loosen the powder.
2. Measure 94 mL of water in a graduated cylinder.
3. Add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute.
4. Add the remainder of water and shake the closed bottle well for about 1 minute.
5. Remove the child-resistant cap and push bottle adapter into neck of bottle.
6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

Dispense with patient instruction sheet and oral dispensers. It is recommended to write the date of expiration of the constituted suspension on the bottle label. (The shelf-life of the constituted suspension is 60 days.)

After constitution the oral suspension contains 200 mg/mL mycophenolate mofetil. Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze. Discard any unused portion 60 days after constitution.

## CellCept Intravenous

### Adults

CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension recommended for patients unable to take oral CellCept. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CellCept Intravenous must be reconstituted and diluted to a concentration of 6 mg/mL using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS by either peripheral or central vein.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION (see **WARNINGS**).

### Preparation of Infusion Solution (6 mg/mL)

Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid direct contact of the prepared solution of CellCept Intravenous with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water (see **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS,** and **HANDLING AND DISPOSAL**).

CellCept Intravenous does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions. Additionally, this product is sealed under vacuum and should retain a vacuum throughout its shelf life. If a lack of vacuum in the vial is noted while adding diluent, the vial should not be used.

CellCept Intravenous infusion solution must be prepared in two steps: the first step is a reconstitution step with 5% Dextrose Injection USP, and the second step is a dilution step with 5% Dextrose Injection USP. A detailed description of the preparation is given below:

Step 1

a) Two (2) vials of CellCept Intravenous are used for preparing each 1 g dose, whereas three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial by injecting 14 mL of 5% Dextrose Injection USP.
b) Gently shake the vial to dissolve the drug.
c) Inspect the resulting slightly yellow solution for particulate matter and discoloration prior to further dilution. Discard the vials if particulate matter or discoloration is observed.

Step 2

a) To prepare a 1 g dose, further dilute the contents of the two reconstituted vials (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL) into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions is 6 mg mycophenolate mofetil per mL.
b) Inspect the infusion solution for particulate matter or discoloration. Discard the infusion solution if particulate matter or discoloration is observed.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours from reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CellCept Intravenous should not be mixed or administered concurrently via the same infusion catheter with other intravenous drugs or infusion admixtures.

### Dosage Adjustments

In renal transplant patients with severe chronic renal impairment (GFR <25 mL/min/1.73 $m^2$) outside the immediate posttransplant period, doses of CellCept greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **PRECAUTIONS: Patients with Renal Impairment**).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. CellCept may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

If neutropenia develops (ANC <1.3 x $10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **WARNINGS: Neutropenia, ADVERSE REACTIONS,** and **PRECAUTIONS: Laboratory Tests**).

## HANDLING AND DISPOSAL

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits (see **Pregnancy and WARNINGS: Embryofetal Toxicity**). CellCept tablets should not be crushed and CellCept capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in CellCept capsules and CellCept Oral Suspension (before or after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Should a spill occur, wipe up using paper towels wetted with water to remove spilled powder or suspension. Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid direct contact of the prepared solution of CellCept Intravenous with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

## HOW SUPPLIED

### CellCept (mycophenolate mofetil capsules) 250 mg

Blue-brown, two-piece hard gelatin capsules, printed in black with “CellCept 250” on the blue cap and “Roche” on the brown body. Supplied in the following presentations:

| NDC Number | Size |
|---|---|
| NDC 0004-0259-01 | Bottle of 100 |
| NDC 0004-0259-05 | Package containing 12 bottles of 120 |
| NDC 0004-0259-43 | Bottle of 500 |

#### Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

### CellCept (mycophenolate mofetil tablets) 500 mg

Lavender-colored, caplet-shaped, film-coated tablets printed in black with “CellCept 500” on one side and “Roche” on the other. Supplied in the following presentations:

| NDC Number | Size |
|---|---|
| NDC 0004-0260-01 | Bottle of 100 |
| NDC 0004-0260-43 | Bottle of 500 |

#### Storage and Dispensing Information

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in light-resistant containers, such as the manufacturer’s original containers.

### CellCept Oral Suspension (mycophenolate mofetil for oral suspension)

Supplied as a white to off-white powder blend for constitution to a white to off-white mixed-fruit flavor suspension. Supplied in the following presentation:

| NDC Number | Size |
|---|---|
| NDC 0004-0261-29 | 225 mL bottle with bottle adapter and 2 oral dispensers |

#### Storage

Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze.

### CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)

Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt in cartons of 4 vials:

| NDC Number |
|---|
| NDC 0004-0298-09 |

## Storage

Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

PI Revised: June 2012