

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CELLCEPT® safely and effectively. See full prescribing information for CELLCEPT®

CELLCEPT® (mycophenolate mofetil) capsules, for oral use

CELLCEPT® (mycophenolate mofetil) tablets, for oral use

CELLCEPT® Oral Suspension (mycophenolate mofetil), for oral suspension

CELLCEPT® Intravenous (mycophenolate mofetil) for injection, for intravenous use

Initial U.S. Approval: 1995

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS

See full prescribing information for complete boxed warning

- Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning [see Warnings and Precautions (5.1)].
- Increased risk of development of lymphoma and other malignancies, particularly of the skin [see Warnings and Precautions (5.2)].
- Increased susceptibility to infections, including opportunistic infections and severe infections with fatal outcomes [see Warnings and Precautions (5.3)].

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.8, 5.10, 5.11) 8/2018
Warnings and Precautions (5.12, 5.13) 2/2019

INDICATIONS AND USAGE

CELLCEPT is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, and should be used in combination with other immunosuppressants. (1)

DOSAGE AND ADMINISTRATION

ADULTS	DOSING
<u>Kidney Transplant</u>	1 g twice daily, orally or intravenously (IV) over no less than 2 h (2.2)
<u>Heart Transplant</u>	1.5 g twice daily orally or IV, over no less than 2 h (2.3)
<u>Liver Transplant</u>	1.5 g twice daily orally or 1 g twice daily IV over no less than 2 h (2.4)
PEDIATRICS	
<u>Kidney Transplant</u>	600 mg/m ² orally twice daily, up to maximum of 2 g daily (2.2)

- CELLCEPT Intravenous is an alternative when patients cannot tolerate oral medication. Administer within 24 hours following transplantation, until patients can tolerate oral medication, up to 14 days. (2.1)
- Reduce or interrupt dosing in the event of neutropenia. (2.5)
- See full prescribing information (FPI) for: adjustments for renal impairment and neutropenia (2.5), preparation of oral suspension and IV solution. (2.6)

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DOSAGE FORMS AND STRENGTHS

- Capsules: 250 mg
- Tablets: 500 mg
- For Suspension: 20 g mycophenolate mofetil, powder for reconstitution
- For Injection: 500 mg mycophenolate mofetil hydrochloride, for single-dose use

CONTRAINDICATIONS

- Hypersensitivity to mycophenolate mofetil, MPA acid or any component of the drug product (4)
- Patients allergic to Polysorbate 80 (present in CELLCEPT IV) (4)

WARNINGS AND PRECAUTIONS

- Blood Dyscrasias (Neutropenia, Red Blood Cell Aplasia): Monitor with blood tests; consider treatment interruption or dose reduction. (5.4)
- Gastrointestinal Complications: Monitor for complications such as bleeding, ulceration and perforations, particularly in patients with underlying gastrointestinal disorders. (5.5)
- Hypoxanthine-Guanine Phosphoribosyl-Transferase Deficiency: Avoid use of CELLCEPT. (5.6)
- Immunizations: Avoid live attenuated vaccines. (5.7)
- Local Reactions with Rapid Intravenous Administration: CELLCEPT Intravenous must not be administered by rapid or bolus intravenous injection. (5.8)
- Phenylketonurics: Oral suspension contains aspartame. (5.9)
- Blood Donation: Avoid during therapy and for 6 weeks thereafter. (5.10)
- Semen Donation: Avoid during therapy and for 90 days thereafter. (5.11)
- Potential Impairment on Driving and Use of Machinery: CELLCEPT may affect ability to drive or operate machinery. (5.13)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials (20 % or greater) include diarrhea, leukopenia, infection, vomiting, and there is evidence of a higher frequency of certain types of infections e.g., opportunistic infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.com

DRUG INTERACTIONS

- See FPI for drugs that may interfere with systemic exposure and reduce CELLCEPT efficacy: antacids with magnesium or aluminum hydroxide, proton pump inhibitors, drugs that interfere with enterohepatic recirculation, telmisartan, calcium-free phosphate binders. (7.1)
- CELLCEPT may reduce effectiveness of oral contraceptives. Use of additional barrier contraceptive methods is recommended. (7.2)
- See FPI for other important drug interactions. (7)

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Safety and effectiveness in allogeneic heart or liver transplants has not been established (8.4)
- Male Patients: Sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment (8.3)

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Revised: 2/2019

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES and SERIOUS INFECTIONS

- **Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning [see Warnings and Precautions (5.1), Use in Special Populations (8.1, 8.3)].**
- **Increased risk of development of lymphoma and other malignancies, particularly of the skin [see Warnings and Precautions (5.2)].**
- **Increased susceptibility to bacterial, viral, fungal and protozoal infections, including opportunistic infections and viral reactivation of hepatitis B and C, which may lead to hospitalizations and fatal outcomes [see Warnings and Precautions (5.3)].**

1 INDICATIONS AND USAGE

CELLCEPT [mycophenolate mofetil (MMF)] is indicated for the prophylaxis of organ rejection, in recipients of allogeneic kidney [see *Clinical Studies (14.1)*], heart [see *Clinical Studies (14.2)*] or liver transplants [see *Clinical Studies (14.3)*], in combination with other immunosuppressants.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

CELLCEPT should not be used without the supervision of a physician with experience in immunosuppressive therapy.

CELLCEPT Capsules, Tablets and Oral Suspension

CELLCEPT oral dosage forms (capsules, tablets or oral suspension) **should not be used interchangeably with mycophenolic acid delayed-release tablets without supervision of a physician with experience in immunosuppressive therapy** because the rates of absorption following the administration of CELLCEPT oral dosage forms and mycophenolic acid delayed-release tablets are not equivalent.

CELLCEPT tablets should not be crushed and CELLCEPT capsules should not be opened or crushed. Patients should avoid inhalation or contact of the skin or mucous membranes with the powder contained in CELLCEPT capsules and oral suspension. If such contact occurs, they must wash the area of contact thoroughly with soap and water. In case of ocular contact, rinse eyes with plain water.

The initial oral dose of CELLCEPT should be given as soon as possible following kidney, heart or liver transplant. It is recommended that CELLCEPT be administered on an empty stomach. In stable transplant patients, however, CELLCEPT may be administered with food if necessary [see *Clinical Pharmacology (12.3)*]. Once reconstituted, CELLCEPT Oral Suspension must not be mixed with any liquids prior to dose administration. If needed, CELLCEPT Oral Suspension can

be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Patients should be instructed to take a missed dose as soon as they remember, except if it is closer than 2 hours to the next scheduled dose; in this case, they should continue to take CELLCEPT at the usual times.

CELLCEPT Intravenous

CELLCEPT Intravenous is recommended for patients unable to take oral CELLCEPT. CELLCEPT Intravenous should be administered within 24 hours following transplant. CELLCEPT Intravenous can be administered for up to 14 days; however, patients should be switched to oral CELLCEPT as soon as they can tolerate oral medication.

CELLCEPT Intravenous must be reconstituted before use [see *Dosage and Administration (2.6)*]. CELLCEPT Intravenous is incompatible with other intravenous infusion solutions and should not be mixed or administered concurrently via the same infusion catheter with other intravenous drugs or infusion admixtures.

CELLCEPT Intravenous must not be administered as a bolus. 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, as rapid infusion increases the risk of local adverse reactions such as phlebitis and thrombosis [see *Adverse Reactions (6.1)*].

2.2 Dosing for Kidney Transplant Patients: Adults and Pediatrics

Adults

The recommended dose for adult kidney transplant patients is 1 g orally or intravenously infused over no less than 2 hours, twice daily (daily dose of 2 g).

Pediatrics (3 months and older)

Pediatric dosing is based on body surface area (BSA). The recommended dose of CELLCEPT oral suspension for pediatric kidney transplant patients 3 months and older is 600 mg/m², administered twice daily (maximum daily dose of 2g or 10 mL of the oral suspension). Pediatric patients with BSA ≥ 1.25 m² may be dosed with capsules or tablets as follows:

Table 1. Pediatric Dosing Using Capsules or Tablets for Pediatric Kidney Transplant

Body Surface Area	Dosing
1.25 m ² to <1.5 m ²	CELLCEPT capsule 750 mg twice daily (1.5 g daily dose)
≥ 1.5 m ²	CELLCEPT capsules or tablets 1 g twice daily (2 g daily dose)

2.3 Dosing for Heart Transplant Patients: Adults

The recommended dose of CELLCEPT for adult heart transplant patients is 1.5 g orally or intravenously infused over no less than 2 hours administered twice daily (daily dose of 3 g).

2.4 Dosing for Liver Transplant Patients: Adults

The recommended dose of CELLCEPT for adult liver transplant patients is 1.5 g administered orally twice daily (daily dose of 3 g) or 1 g infused intravenously over no less than 2 hours, twice daily (daily dose of 2 g).

2.5 Dosing Adjustments: Patients with Renal Impairment, Neutropenia

Renal Impairment

No dose adjustments are needed in kidney transplant patients with delayed graft function postoperatively [*see Clinical Pharmacology (12.3)*]. In kidney transplant patients with severe chronic impairment of the graft (GFR <25 mL/min/1.73 m²), do not administer doses of CELLCEPT greater than 1 g twice a day. These patients should be carefully monitored [*see Clinical Pharmacology (12.3)*].

Neutropenia

If neutropenia develops (ANC <1.3 x 10³/μL), dosing with CELLCEPT should be interrupted or reduced, appropriate diagnostic tests performed, and the patient managed appropriately [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

2.6 Preparation Instructions of Oral Suspension and Intravenous for Pharmacists

General Preparation Instructions Before Handling the Formulations

Mycophenolate mofetil (MMF) has demonstrated teratogenic effects in humans. Follow applicable special handling and disposal procedures.¹ [*see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.1, 8.3), How Supplied/Storage and Handling (16.1)*]

Care should be taken to avoid inhalation or direct contact with skin or mucous membranes of the dry powder or the constituted suspension because MMF has demonstrated teratogenic effects in humans. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table surface after reconstitution. If such contact occurs, wash hands thoroughly with soap and water; rinse eyes with water.

Alert patients that they and others should also avoid inhalation or contact of the skin or mucous membranes with the oral suspension. Advise them to wash the area thoroughly with soap and water if such contact occurs; if ocular contact occurs, rinse eyes with plain water.

CELLCEPT Oral Suspension

CELLCEPT Oral Suspension must be reconstituted by the pharmacist prior to dispensing to the patient. CELLCEPT Oral Suspension should not be mixed with any other medication. After reconstitution, the oral suspension contains 200 mg/mL MMF.

Before proceeding with the reconstitution steps read the general preparation instructions above [*see General Preparation Instructions Before Handling the Formulations*]. The following are the steps for reconstitution:

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 reconstitution 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.
7. Write the date of expiration of the constituted suspension on the bottle label. (The shelf-life of the constituted suspension is 60 days.)
8. Dispense with the “Instruction for Use” and oral dispensers. Alert patients to read the important handling information described in the instructions for use.

Store reconstituted suspension at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Storage in a refrigerator at 2° C to 8°C (36°F to 46°F) is acceptable. Do not freeze. Discard any unused portion 60 days after constitution.

CELLCEPT Intravenous

Before proceeding with the preparation steps for CELLCEPT Intravenous read the general preparation instructions [*see General Preparation Instructions Before Handling the Formulations*] and note the following:

- CELLCEPT Intravenous does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.
- 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 the diluent, the vial should not be used.

CELLCEPT Intravenous must be reconstituted and further diluted. A detailed description of the preparation is given below.

Table 2. Preparation Instructions of CELLCEPT Intravenous for Pharmacists

Preparation of the 1g dose	<ol style="list-style-type: none"> 1. <u>Reconstitute</u> two (2) vials of CELLCEPT Intravenous by injecting 14 mL of 5% Dextrose Injection USP into each vial. 2. Gently shake the vial to dissolve the drug. 3. 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. 4. <u>Dilute</u> the contents of the two reconstituted vials (approximately 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. 5. Inspect the resulting infusion solution and discard if particulate matter or discoloration is observed.
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Preparation of the 1.5 g dose	<ol style="list-style-type: none"> 1. <u>Reconstitute</u> three (3) vials of CELLCEPT Intravenous by injecting 14 mL of 5% Dextrose Injection USP into each vial. 2. Gently shake the vial to dissolve the drug. 3. 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. 4. <u>Dilute</u> the contents of the three reconstituted vials (approximately 3 x 15 mL) into 210 mL of 5% Dextrose Injection USP. 5. Inspect the resulting infusion solution and discard if particulate matter or discoloration is observed.
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The administration of the infusion should be initiated within 4 hours of reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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

3 DOSAGE FORMS AND STRENGTHS

CELLCEPT is available in the following dosage forms and strengths:

Capsules	250 mg mycophenolate mofetil, two-piece hard gelatin capsules, blue-brown, “CELLCEPT 250” printed in black on the blue cap and “Roche” on the brown body
Tablets	500 mg mycophenolate mofetil, lavender-colored, caplet-shaped, film-coated tablets printed in black with “CELLCEPT 500” on one side and “Roche” on the other
For suspension	mycophenolate mofetil white to off-white powder, 200 mg/mL upon reconstitution.
For injection	500 mg mycophenolate mofetil white to off-white lyophilized powder, in a single-dose vial for reconstitution

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Embryofetal Toxicity

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, kidney and nervous system. Females of reproductive potential must be made aware of these risks and must be counseled regarding pregnancy prevention and planning. Avoid use of MMF during pregnancy if safer treatment options are available [see *Use in Specific Populations (8.1, 8.3)*].

5.2 Lymphoma and Other Malignancies

Patients receiving immunosuppressants, including CELLCEPT, are at increased risk of developing lymphomas and other malignancies, particularly of the skin [see *Adverse Reactions (6.1)*]. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. 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.

Post-transplant lymphoproliferative disorder (PTLD) developed in 0.4% to 1% of patients receiving CELLCEPT (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of kidney, heart and liver transplant patients [see *Adverse Reactions (6.1)*]. The majority of PTLD cases appear to be related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children. In pediatric patients, no other malignancies besides PTLD were observed in clinical trials [see *Adverse Reactions (6.1)*].

5.3 Serious Infections

Patients receiving immunosuppressants, including CELLCEPT, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. The risk increases with the total immunosuppressive load. These infections may lead to serious outcomes, including hospitalizations and death [see *Adverse Reactions (6.1), (6.2)*].

Serious viral infections reported include:

- Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infection
- JC virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.
- Viral reactivation in patients infected with Hepatitis B and C

Consider reducing immunosuppression in patients who develop new infections or reactivate viral infections, weighing the risk that reduced immunosuppression represents to the functioning allograft.

PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss [see *Adverse Reactions (6.2)*]. Patient monitoring may help detect patients at risk for PVAN.

PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia [see *Adverse Reactions (6.2)*]. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms.

The risk of CMV viremia and CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease.

Viral reactivation has been reported in patients infected with HBV or HCV. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

5.4 Blood Dyscrasias: Neutropenia and Pure Red Cell Aplasia (PRCA)

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$] developed in transplant patients receiving CELLCEPT 3 g daily [see *Adverse Reactions (6.1)*]. Patients receiving CELLCEPT should be monitored for neutropenia. Neutropenia has been observed most frequently in the period from 31 to 180 days post-transplant in patients treated for prevention of kidney, heart and liver rejection. The development of neutropenia may be related to CELLCEPT itself, concomitant medications, viral infections, or a combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3/\mu\text{L}$), dosing with CELLCEPT should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately [see *Dosage and Administration (2.5)*].

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

Consider monitoring with complete blood counts weekly for the first month, twice monthly for the second and third months, and monthly for the remainder of the first year.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CELLCEPT in combination with other immunosuppressive agents. 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.

5.5 Gastrointestinal Complications

Gastrointestinal bleeding requiring hospitalization, ulceration and perforations were observed in clinical trials. Physicians should be aware of these serious adverse effects particularly when administering CELLCEPT to patients with a gastrointestinal disease.

5.6 Patients with Hypoxanthine-Guanine Phosphoribosyl-Transferase Deficiency (HGPRT)

CELLCEPT is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; therefore it should be avoided in patients with hereditary deficiencies of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndromes because it may cause an exacerbation of disease symptoms characterized by the overproduction and accumulation of uric acid leading to symptoms associated with gout such as acute arthritis, tophi, nephrolithiasis or urolithiasis and renal disease including renal failure.

5.7 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. Advise patients to discuss with the physician before seeking any immunizations.

5.8 Local Reactions with Rapid Intravenous Administration

CELLCEPT Intravenous solution must not be administered by rapid or bolus intravenous injection as rapid infusion increases the risk of local adverse reactions such as phlebitis and thrombosis [see *Adverse Reactions (6.1)*].

5.9 Risks in Patients with Phenylketonuria

Phenylalanine can be harmful to patients with phenylketonuria (PKU). CELLCEPT Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Before prescribing CELLCEPT Oral Suspension to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including CELLCEPT.

5.10 Blood Donation

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of CELLCEPT because their blood or blood products might be administered to a female of reproductive potential or a pregnant woman.

5.11 Semen Donation

Based on animal data, men should not donate semen during therapy and for 90 days following discontinuation of CELLCEPT [see *Use In Specific Populations (8.3)*].

5.12 Effect of Concomitant Medications on Mycophenolic Acid Concentrations

A variety of drugs have potential to alter systemic MPA exposure when co-administered with CELLCEPT. Therefore, determination of MPA concentrations in plasma before and after making any changes to immunosuppressive therapy, or when adding or discontinuing concomitant medications, may be appropriate to ensure MPA concentrations remain stable.

5.13 Potential Impairment of Ability to Drive or Operate Machinery

CELLCEPT may impact the ability to drive and use machines. Patients should avoid driving or using machines if they experience somnolence, confusion, dizziness, tremor, or hypotension during treatment with CELLCEPT [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Embryofetal Toxicity [see *Warnings and Precautions (5.1)*]
- Lymphomas and Other Malignancies [see *Warnings and Precautions (5.2)*]
- Serious Infections [see *Warnings and Precautions (5.3)*]
- Blood Dyscrasias: Neutropenia, Pure Red Cell Aplasia [see *Warnings and Precautions (5.4)*]

- Gastrointestinal Complications [see Warnings and Precautions (5.5)]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

An estimated total of 1557 patients received CELLCEPT during pivotal clinical trials in the prevention of acute organ rejection. Of these, 991 were included in the three renal studies, 277 were included in one hepatic study, and 289 were included in one cardiac study. Patients in all study arms also received cyclosporine and corticosteroids.

The data described below primarily derive from five randomized, active-controlled double-blind 12-month trials of CELLCEPT in *de novo* kidney (3) heart (1) and liver (1) transplant patients [see Clinical Studies (14.1, 14.2 and 14.3)].

CELLCEPT Oral

The incidence of adverse reactions for CELLCEPT was determined in five randomized, comparative, double-blind trials in the prevention of rejection in kidney, heart and liver transplant patients (two active- and one placebo-controlled trials, one active-controlled trial, and one active-controlled trial, respectively) [see Clinical Studies (14.1, 14.2 and 14.3)].

The three *de novo* kidney studies with 12-month duration compared two dose levels of oral CELLCEPT (1 g twice daily and 1.5 g twice daily) 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 anti-thymocyte globulin (ATGAM®) induction therapy.

In the *de novo* heart transplantation study with 12-month duration, patients received CELLCEPT 1.5 g twice daily (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.

In the *de novo* liver transplantation study with 12-month duration, patients received CELLCEPT 1 g twice daily intravenously for up to 14 days followed by CELLCEPT 1.5 g twice daily 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 total number of patients enrolled was 565.

Approximately 53% of the kidney transplant patients, 65% of the heart transplant patients, and 48% of the liver transplant patients were treated for more than 1 year. Adverse reactions reported in $\geq 20\%$ of patients in the CELLCEPT treatment groups are presented below. The safety data of three kidney transplantation studies are pooled together.

Table 3. Adverse Reactions in Controlled Studies of De Novo Kidney, Heart or Liver Transplantation Reported in $\geq 20\%$ of Patients in the CELLCEPT Group

Adverse drug reaction	Kidney Studies			Heart Study		Liver Study	
	CellCept	AZA	Placebo	CellCept	AZA	CellCept	AZA

(MedDRA) System Organ Class	2g/day (n=501) or 3g/day (n=490)	1 to 2 mg/kg/day or 100 to 150 mg/day		3g/day	1.5 to 3 mg/kg/day	3g/day	1 to 2 mg/kg/day
	(n=991)	(n=326)	(n=166)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Infections and infestations							
Bacterial infections	39.9	33.7	37.3	-	-	27.4	26.5
Viral infections	- ^a	-	-	31.1	24.9	-	-
Blood and lymphatic system disorders							
Anemia	20.0	23.6	2.4	45.0	47.1	43.0	53.0
Ecchymosis	-	-	-	20.1	9.7	-	-
Leukocytosis	-	-	-	42.6	37.4	22.4	21.3
Leukopenia	28.6	24.8	4.2	34.3	43.3	45.8	39.0
Thrombocytopenia	-	-	-	24.2	28.0	38.3	42.2
Metabolism and nutrition disorders							
Hypercholesterolemia	-	-	-	46.0	43.9	-	-
Hyperglycemia	-	-	-	48.4	53.3	43.7	48.8
Hyperkalemia	-	-	-	-	-	22.0	23.7
Hypocalcemia	-	-	-	-	-	30.0	30.0
Hypokalemia	-	-	-	32.5	26.3	37.2	41.1
Hypomagnesemia	-	-	-	20.1	14.2	39.0	37.6
Psychiatric disorders							
Depression	-	-	-	20.1	15.2	-	-
Insomnia	-	-	-	43.3	39.8	52.3	47.0
Nervous system disorders							
Dizziness	-	-	-	34.3	33.9	-	-
Headache	-	-	-	58.5	55.4	53.8	49.1
Tremor	-	-	-	26.3	25.6	33.9	35.5
Cardiac disorders							
Tachycardia	-	-	-	22.8	21.8	22.0	15.7
Vascular disorders							
Hypertension	27.5	32.2	19.3	78.9	74.0	62.1	59.6
Hypotension	-	-	-	34.3	40.1	-	-
Respiratory, thoracic and mediastinal disorders							
Cough	-	-	-	40.5	32.2	-	-
Dyspnea	-	-	-	44.3	44.3	31.0	30.3
Pleural effusion	-	-	-	-	-	34.3	35.9
Gastrointestinal disorders							
Abdominal pain	22.4	23.0	11.4	41.9	39.4	62.5	51.2
Constipation	-	-	-	43.6	38.8	37.9	38.3

Decreased appetite	-	-	-	-	-	25.3	17.1
Diarrhea	30.4	20.9	13.9	52.6	39.4	51.3	49.8
Dyspepsia	-	-	-	22.1	22.1	22.4	20.9
Nausea	-	-	-	56.1	60.2	54.5	51.2
Vomiting	-	-	-	39.1	34.6	32.9	33.4
Hepatobiliary disorders							
Blood lactate dehydrogenase increased	-	-	-	23.5	18.3	-	-
Hepatic enzyme increased	-	-	-	-	-	24.9	19.2
Skin and subcutaneous tissues disorders							
Rash	-	-	-	26.0	20.8	-	-
Renal and urinary disorders							
Blood creatinine increased	-	-	-	42.2	39.8	-	-
Blood urea increased	-	-	-	36.7	34.3	-	-
General disorders and administration site conditions							
Asthenia	-	-	-	49.1	41.2	35.4	33.8
Edema ^b	21.0	28.2	8.4	67.5	55.7	48.4	47.7
Pain ^c	24.8	32.2	9.6	79.2	77.5	74.0	77.5
Pyrexia	-	-	-	56.4	53.6	52.3	56.1

^a: “-” Indicates that the incidence was below the cutoff value of 20% for inclusion in the table.

^b: “Edema” includes peripheral edema, facial edema, scrotal edema.

^c: “Pain” includes musculoskeletal pain (myalgia, neck pain, back pain).

In the three *de novo* kidney studies, patients receiving 2 g/day of CELLCEPT had an overall better safety profile than did patients receiving 3 g/day of CELLCEPT.

Post-transplant lymphoproliferative disease (PTLD, pseudolymphoma) 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 kidney, heart and liver transplant patients followed for at least 1 year [see *Warnings and Precautions* (5.2)]. 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 kidney and heart transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. In pediatric patients, PTLD was observed in 1.35% (2/148) by 12 months post-transplant.

Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia are a known risk associated with mycophenolate and may lead or contribute to the occurrence of infections and hemorrhages [see *Warnings and Precautions* (5.3)]. Severe neutropenia (ANC <0.5 x 10³/μL) developed in up to 2% of kidney transplant patients, up to 2.8% of heart transplant patients and up to 3.6% of liver transplant patients receiving CELLCEPT 3 g daily [see *Warnings and Precautions* (5.4) and *Dosage and Administration* (2.5)].

The most common opportunistic infections in patients receiving CELLCEPT with other immunosuppressants were mucocutaneous candida, CMV viremia/syndrome, and herpes simplex. The proportion of patients with CMV viremia/syndrome was 13.5%. In patients receiving CELLCEPT (2 g or 3 g) in controlled studies for prevention of kidney, heart or liver rejection, fatal infection/sepsis occurred in approximately 2% of kidney and heart patients and in 5% of liver patients [see Warnings and Precautions (5.3)].

The most serious gastrointestinal disorders reported were ulceration and hemorrhage, which are known risks associated with CELLCEPT. Mouth, esophageal, gastric, duodenal, and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials, while the most common gastrointestinal disorders were diarrhea, nausea and vomiting. Endoscopic investigation of patients with CELLCEPT-related diarrhea revealed isolated cases of intestinal villous atrophy [see Warnings and Precautions (5.5)].

The following adverse reactions were reported with 3% to <20% incidence in kidney, heart, and liver transplant patients treated with CELLCEPT, in combination with cyclosporine and corticosteroids.

Table 4. Adverse Reactions in Controlled Studies of De Novo Kidney, Heart or Liver Transplantation Reported in 3% to <20% of Patients Treated with CELLCEPT in Combination with Cyclosporine and Corticosteroids

System Organ Class	Adverse Reactions
Body as a Whole	cellulitis, chills, hernia, malaise
Infections and Infestations	fungal infections
Hematologic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia
Urogenital	hematuria
Cardiovascular	hypotension
Metabolic and Nutritional	acidosis, alkaline phosphatase increased, hyperlipemia, hypophosphatemia, weight loss
Digestive	esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, hepatitis, ileus, nausea and vomiting, stomach ulcer, stomatitis
Neoplasm benign, malignant and unspecified	neoplasm

System Organ Class	Adverse Reactions
Skin and Appendages	skin benign neoplasm, skin carcinoma
Psychiatric	confusional state
Nervous	hypertonia, paresthesia, somnolence
Musculoskeletal	arthralgia, myasthenia

Pediatric Study

The type and frequency of adverse events in a clinical study for prevention of kidney allograft rejection in 100 pediatric patients 3 months to 18 years of age dosed with CELLCEPT oral suspension 600 mg/m² twice daily (up to 1 g twice daily) were generally similar to those observed in adult patients dosed with CELLCEPT capsules at a dose of 1 g twice daily 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.

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 Warnings and Precautions (5.3) and Adverse Reactions (6.1)*].

CELLCEPT Intravenous

The safety 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 kidney transplant patients in the immediate post-transplant period (administered for the first 5 days). The potential venous irritation of CELLCEPT Intravenous was evaluated by comparing the adverse reactions attributable to peripheral venous infusion of CELLCEPT Intravenous with those observed in the intravenous placebo group; patients in the placebo group received active medication by the oral route.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of CELLCEPT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- **Embryo-Fetal Toxicity:** Congenital malformations and spontaneous abortions, mainly in the first trimester, have been reported following exposure to mycophenolate mofetil (MMF) in combination with other immunosuppressants during pregnancy [*see Warnings and Precautions (5.1), and Use in Specific Populations (8.1), (8.3)*]. Congenital malformations include:
 - Facial malformations: cleft lip, cleft palate, micrognathia, hypertelorism of the orbits
 - Abnormalities of the ear and eye: abnormally formed or absent external/middle ear, coloboma, microphthalmos
 - Malformations of the fingers: polydactyly, syndactyly, brachydactyly
 - Cardiac abnormalities: atrial and ventricular septal defects
 - Esophageal malformations: esophageal atresia
 - Nervous system malformations: such as spina bifida.
- **Cardiovascular:** Venous thrombosis has been reported in patients treated with CELLCEPT administered intravenously.
- **Digestive:** Colitis, pancreatitis
- **Hematologic and Lymphatic:** Bone marrow failure, cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with CELLCEPT in combination with other immunosuppressive agents [*see Warnings and Precautions (5.4)*].
- **Immune:** Hypersensitivity, hypogammaglobinemia.
- **Infections:** Meningitis, infectious endocarditis, tuberculosis, atypical mycobacterial infection, progressive multifocal leukoencephalopathy, BK virus infection, viral reactivation of hepatitis B and hepatitis C, protozoal infections [*see Warnings and Precautions (5.3)*].
- **Respiratory:** Bronchiectasis, interstitial lung disease, 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 post-transplant patients receiving CELLCEPT.
- **Vascular:** Lymphocele

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on CELLCEPT

Table 5. Drug Interactions with CELLCEPT that Affect Mycophenolic Acid (MPA) Exposure

Antacids with Magnesium or Aluminum Hydroxide
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<i>Clinical Impact</i>	Concomitant use with an antacid containing magnesium or aluminum hydroxide decreases MPA systemic exposure [see <i>Clinical Pharmacology (12.3)</i>], which may reduce CELLCEPT efficacy.
<i>Prevention or Management</i>	Administer magnesium or aluminum hydroxide containing antacids at least 2h after CELLCEPT administration.
Proton Pump Inhibitors (PPIs)	
<i>Clinical Impact</i>	Concomitant use with PPIs decreases MPA systemic exposure [see <i>Clinical Pharmacology (12.3)</i>], which may reduce CELLCEPT efficacy.
<i>Prevention or Management</i>	Monitor patients for alterations in efficacy when PPIs are co-administered with CELLCEPT.
<i>Examples</i>	Lansoprazole, pantoprazole
Drugs that Interfere with Enterohepatic Recirculation	
<i>Clinical Impact</i>	Concomitant use with drugs that directly interfere with enterohepatic recirculation, or indirectly interfere with enterohepatic recirculation by altering the gastrointestinal flora, can decrease MPA systemic exposure [see <i>Clinical Pharmacology (12.3)</i>], which may reduce CELLCEPT efficacy.
<i>Prevention or Management</i>	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
<i>Examples</i>	Trimethoprim/sulfamethoxazole, bile acid sequestrants (cholestyramine), rifampin as well as aminoglycoside, cephalosporin, fluoroquinolone and penicillin classes of antimicrobials
Drugs Modulating Glucuronidation	
<i>Clinical Impact</i>	Concomitant use with drugs inducing glucuronidation decreases MPA systemic exposure, potentially reducing CELLCEPT efficacy, while use with drugs inhibiting glucuronidation increases MPA systemic exposure [see <i>Clinical Pharmacology (12.3)</i>], which may increase the risk of CELLCEPT related adverse reactions.
<i>Prevention or Management</i>	Monitor patients for alterations in efficacy or CELLCEPT related adverse reactions when these drugs are co-administered with CELLCEPT.
<i>Examples</i>	Telmisartan (induces glucuronidation); isavuconazole (inhibits glucuronidation).
Calcium Free Phosphate Binders	

<i>Clinical Impact</i>	Concomitant use with calcium free phosphate binders decrease MPA systemic exposure [see <i>Clinical Pharmacology (12.3)</i>], which may reduce CELLCEPT efficacy.
<i>Prevention or Management</i>	Administer calcium free phosphate binders at least 2 hours after CELLCEPT.
<i>Examples</i>	Sevelamer

7.2 Effect of CELLCEPT on Other Drugs

Table 6. Drug Interactions with CELLCEPT that Affect Other Drugs

Drugs that Undergo Renal Tubular Secretion	
<i>Clinical Impact</i>	When concomitantly used with CELLCEPT, its metabolite MPAG, may compete with drugs eliminated by renal tubular secretion which may increase plasma concentrations and/or adverse reactions associated with these drugs.
<i>Prevention or Management</i>	Monitor for drug-related adverse reactions in patients with renal impairment.
<i>Examples</i>	Acyclovir, ganciclovir, probenecid, valacyclovir, valganciclovir
Combination Oral Contraceptives	
<i>Clinical Impact</i>	Concomitant use with CELLCEPT decreased the systemic exposure to levonorgestrel, but did not affect the systemic exposure to ethinylestradiol [see <i>Clinical Pharmacology (12.3)</i>], which may result in reduced combination oral contraceptive effectiveness.
<i>Prevention or Management</i>	Use additional barrier contraceptive methods.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to mycophenolate during pregnancy and those becoming pregnant within 6 weeks of discontinuing CELLCEPT treatment. To report a pregnancy or obtain information about the registry, visit www.mycophenolateREMS.com or call 1-800-617-8191.

Risk Summary

Use of mycophenolate mofetil (MMF) during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of multiple congenital malformations in multiple organ systems [see *Human Data*]. Oral administration of mycophenolate to rats and rabbits during the period of organogenesis produced congenital malformations and pregnancy

loss at doses less than the recommended clinical dose (0.02 to 0.1 times the recommended clinical doses in kidney and heart transplant patients) [*see Animal Data*].

Consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CELLCEPT should be discussed with the pregnant woman.

The estimated background risk of pregnancy loss and congenital malformations in organ transplant populations is not clear. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

A spectrum of congenital malformations (including multiple malformations in individual newborns) has been reported in 23 to 27% of live births in MMF exposed pregnancies, based on published data from pregnancy registries. Malformations that have been documented include external ear, eye, and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney, and nervous system.

Based on published data from pregnancy registries, the risk of first trimester pregnancy loss has been reported at 45 to 49% following MMF exposure.

Animal Data

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Oral administration of MMF to pregnant rats from Gestational Day 7 to Day 16 produced increased embryofetal lethality and fetal malformations including anophthalmia, agnathia, and hydrocephaly at doses equivalent to 0.03 and 0.02 times the recommended human doses for renal and cardiac transplant patients, respectively, when corrected for BSA. Oral administration of MMF to pregnant rabbits from Gestational Day 7 to Day 19 produced increased embryofetal lethality and fetal malformations included ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia at dose equivalents as low as 0.1 and 0.06 times the recommended human doses for renal and cardiac transplant patients, respectively, when corrected for BSA.

8.2 Lactation

Risk Summary

There are no data on the presence of mycophenolate in human milk, or the effects on milk production. There are limited data in the National Transplantation Pregnancy Registry on the effects of mycophenolate on a breastfed child [*see Data*]. Studies in rats treated with MMF have shown mycophenolic acid (MPA) to be present in milk. Because available data are limited, it is not possible to exclude potential risks to a breastfeeding infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CELLCEPT and any potential adverse effects on the breastfed infant from CELLCEPT or from the underlying maternal condition.

Data

Limited information is available from the National Transplantation Pregnancy Registry. Of seven infants reported by the National Transplantation Pregnancy Registry to have been breastfed while the mother was taking mycophenolate, all were born at 34-40 weeks gestation, and breastfed for up to 14 months. No adverse events were reported.

8.3 Females and Males of Reproductive Potential

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.

Pregnancy Planning

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

Pregnancy Testing

To prevent unplanned exposure during pregnancy, all 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, consider alternative immunosuppressants with less potential for embryofetal toxicity whenever possible.

Contraception

Female Patients

Females of reproductive potential taking CELLCEPT must receive contraceptive counseling and use acceptable contraception (see **Table 7** for acceptable contraception methods). Patients must use acceptable birth control during the entire CELLCEPT therapy, and for 6 weeks after stopping CELLCEPT, unless the patient chooses abstinence.

Patients should be aware that CELLCEPT reduces blood levels of the hormones from the oral contraceptive pill and could theoretically reduce its effectiveness [see *Drug Interactions (7.2)*].

Table 7. Acceptable Contraception Methods For Females Of Reproductive Potential

Pick from the following birth control options:

Option 1	
Methods to Use Alone	<ul style="list-style-type: none"> • Intrauterine devices (IUDs) • Tubal sterilization • Patient’s partner vasectomy

OR

Option 2	Hormone Methods choose 1		Barrier Methods choose 1
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Choose One Hormone Method AND One Barrier Method	Estrogen and Progesterone <ul style="list-style-type: none"> • Oral Contraceptive Pill • Transdermal patch • Vaginal ring Progesterone-only <ul style="list-style-type: none"> • Injection • Implant 	AND	<ul style="list-style-type: none"> • Diaphragm with spermicide • Cervical cap with spermicide • Contraceptive sponge • Male condom • Female condom
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OR

Option 3	Barrier Methods choose 1		Barrier Methods choose 1
Choose One Barrier Method from each column <i>(must choose two methods)</i>	<ul style="list-style-type: none"> • Diaphragm with spermicide • Cervical cap with spermicide • Contraceptive sponge 	AND	<ul style="list-style-type: none"> • Male condom • Female condom

Male Patients

Genotoxic effects have been observed in animal studies at exposures exceeding the human therapeutic exposures by approximately 2.5 times. Thus, the risk of genotoxic effects on sperm cells cannot be excluded. Based on this potential risk, sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment. Also, based on the potential risk of genotoxic effects, male patients should not donate sperm during treatment with CELLCEPT and for at least 90 days after cessation of treatment [see *Use in Special Populations (8.1)*, *Nonclinical Toxicology (13.1)*, *Patient Counseling Information (17.9)*].

8.4 Pediatric Use

Safety and effectiveness of CELLCEPT have been established in pediatric patients 3 months and older for the prophylaxis of kidney rejection after allogeneic kidney transplant. Use of CELLCEPT in this population is supported by evidence from adequate and well-controlled studies of CELLCEPT in adults with additional data from one open-label, pharmacokinetic and safety study of CELLCEPT in pediatric patients after receiving allogeneic kidney transplant [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, *Clinical Studies (14.1)*].

Safety and effectiveness in pediatric patients receiving allogeneic heart or liver transplants have not been established.

8.5 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 take into consideration the presence of decreased hepatic, renal or cardiac function and of concomitant drug therapies. [see *Adverse Reactions (6.1)*, *Drug Interactions (7)*].

8.6 Patients with Renal Impairment

Patients with Kidney Transplant

No dose adjustments are needed in kidney transplant patients experiencing delayed graft function postoperatively but patients should be carefully monitored [see *Clinical Pharmacology (12.3)*]. In kidney transplant patients with severe chronic impairment of the graft (GFR <25 mL/min/1.73 m²), no dose adjustments are necessary; however, doses greater than 1 g administered twice a day should be avoided.

Patients with Heart and Liver Transplant

No data are available for heart or liver transplant patients with severe chronic renal impairment. CELLCEPT may be used for heart or liver transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

8.7 Patients with Hepatic Impairment

Patients with Kidney Transplant

No dose adjustments are recommended for kidney transplant 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 (12.3)*].

Patients with Heart Transplant

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

10 OVERDOSAGE

Possible signs and symptoms of acute overdose include hematological abnormalities such as leukopenia and neutropenia, and gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, vomiting, and dyspepsia.

The experience with overdose of CELLCEPT in humans is limited. The reported effects associated with overdose fall within the known safety profile of the drug. The highest dose administered to kidney transplant patients in clinical trials has been 4 g/day. In limited experience with heart and liver 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, particularly neutropenia [see *Warnings and Precautions (5.4)*].

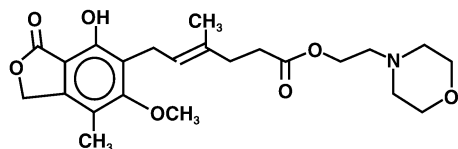
Treatment and Management

MPA and the phenolic glucuronide metabolite of MPA (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 (12.3)*].

11 DESCRIPTION

CELLCEPT (mycophenolate mofetil) is an antimetabolite immunosuppressant. It 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 C₂₃H₃₁NO₇, a molecular weight of 433.50, and the following structural formula:



MMF 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 MMF are 5.6 for the morpholino group and 8.5 for the phenolic group.

MMF 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 MMF, tablets containing 500 mg of MMF, and as a powder for oral suspension which, when reconstituted, contains 200 mg/mL of MMF.

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 croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone (K-90), Opadry® lavender Y-5R-10272-A (hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, polyethylene glycol

400, FD&C Blue No. 2 aluminum lake [indigo carmine aluminum lake], and red iron oxide), talc, Opacode black S-1-17838 (black iron 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 MMF. The chemical name for the hydrochloride salt of MMF 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 MMF hydrochloride for administration by intravenous infusion only. Each vial of CELLCEPT Intravenous contains the equivalent of 500 mg MMF 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 MMF, 6 mg/mL [see *Dosage and Administration* (2.6)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mycophenolate mofetil (MMF) is absorbed following oral administration and hydrolyzed to mycophenolic acid (MPA), the active metabolite. MPA is a 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. MMF 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.

12.2 Pharmacodynamics

There is a lack of information regarding the pharmacodynamic effects of MMF.

12.3 Pharmacokinetics

Absorption

Following oral and intravenous administration, MMF undergoes complete conversion to MPA, the active metabolite. In 12 healthy volunteers, the mean absolute bioavailability of oral MMF relative to intravenous MMF was 94%. Two 500 mg CELLCEPT tablets have been shown to be bioequivalent to four 250 mg CELLCEPT capsules. Five mL of the 200 mg/mL constituted CELLCEPT oral suspension have been shown to be bioequivalent to four 250 mg capsules.

The mean (\pm SD) pharmacokinetic parameters estimates for MPA following the administration of MMF given as single doses to healthy volunteers, and multiple doses to kidney, heart, and liver transplant patients, are shown in **Table 8**. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in kidney transplant patients receiving multiple oral doses of MMF up to a daily dose of 3 g (1.5g twice daily) (see **Table 8**).

Table 8. Pharmacokinetic Parameters for MPA [mean (\pm SD)] Following Administration of MMF to Healthy Volunteers (Single Dose), and Kidney, Heart, and Liver Transplant Patients (Multiple Doses)

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

^aAUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

In the early post-transplant period (less than 40 days post-transplant), kidney, heart, and liver 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 (i.e., 3 to 6 months post-transplant) (non-stationarity in MPA pharmacokinetics).

Mean MPA AUC values following administration of 1 g twice daily intravenous CELLCEPT over 2 hours to kidney transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate post-transplant phase.

In liver transplant patients, administration of 1 g twice daily intravenous CELLCEPT followed by 1.5 g twice daily oral CELLCEPT resulted in mean MPA AUC estimates similar to those found in kidney transplant patients administered 1 g CELLCEPT twice daily.

Effect of Food

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of MMF when administered at doses of 1.5 g twice daily to kidney transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food [*see Dosage and Administration (2.1)*].

Distribution

The mean (\pm SD) apparent volume of distribution of MPA in 12 healthy volunteers was approximately 3.6 (\pm 1.5) L/kg. At clinically relevant concentrations, MPA is 97% bound to plasma albumin. The phenolic glucuronide metabolite of MPA (MPAG) is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable kidney transplant patients; however, at higher MPAG concentrations (observed in patients with kidney impairment or delayed kidney 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 human serum albumin) and MPAG (at \geq 460 mcg/mL with plasma proteins) increased the free fraction of MPA. MPA at concentrations as high as 100 mcg/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%.

Elimination

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

Metabolism

The parent drug, MMF, can be measured systemically during the intravenous infusion; however, approximately 5 minutes after the infusion is stopped or after oral administration, MMF concentrations are below the limit of quantitation (0.4 mcg/mL).

Metabolism to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form MPAG, which is not pharmacologically active. *In vivo*, MPAG is converted to MPA during enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of MMF to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Due to the enterohepatic recirculation of MPAG/MPA, secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours post-dose. Bile sequestrants, such as cholestyramine, reduce MPA AUC by interfering with this enterohepatic recirculation of the drug [see *Overdose (10) and Drug Interaction Studies below*].

Excretion

Negligible amount of drug is excreted as MPA (less than 1% of dose) in the urine. Orally administered radiolabeled MMF 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 mcg/mL), small amounts of MPAG are removed.

Increased plasma concentrations of MMF metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency [see *Specific Populations*].

Specific Populations

Patients with Renal Impairment

The mean (\pm SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with renal impairment are presented in **Table 9**.

In a single-dose study, MMF was administered as a capsule or as an intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment (GFR < 25 mL/min/1.73 m²) was about 75% higher relative to that observed in healthy volunteers (GFR > 80 mL/min/1.73 m²). 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 m²) was 62.4 mcg•h/mL (\pm 19.3). Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied.

Patients with Delayed Graft Function or Nonfunction

In patients with delayed renal graft function post-transplant, mean MPA AUC(0-12h) was comparable to that seen in post-transplant 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 post-transplant patients without delayed renal graft function [*see Dosage and Administration (2.5)*].

In eight patients with primary graft non-function following kidney 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 MMF are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (> 100 mcg/mL), hemodialysis removes only small amounts of MPAG.

Patients with Hepatic Impairment

The mean (\pm SD) pharmacokinetic parameters for MPA following the administration of oral MMF given as single doses to non-transplant subjects with hepatic impairment is presented in **Table 9**.

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. 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 mcg•h/mL (\pm 15.5).

Table 9. Pharmacokinetic Parameters for MPA [mean (\pm SD)] Following Single Doses of MMF Capsules in Chronic Renal and Hepatic Impairment

Pharmacokinetic Parameters for Renal Impairment				
	Dose	T_{max} (h)	C_{max} (mcg/mL)	AUC(0-96h) (mcg•h/mL)
Healthy Volunteers GFR greater than 80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	25.3 (\pm 7.99)	45.0 (\pm 22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	26.0 (\pm 3.82)	59.9 (\pm 12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	19.0 (\pm 13.2)	52.9 (\pm 25.5)
Severe Renal Impairment GFR less than 25 mL/min/1.73 m ² (n=7)	1 g	1.00 (\pm 0.41)	16.3 (\pm 10.8)	78.6 (\pm 46.4)
Pharmacokinetic Parameters for Hepatic Impairment				
	Dose	T_{max} (h)	C_{max} (mcg/mL)	AUC(0-48h) (mcg•h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (\pm 0.14)	24.3 (\pm 5.73)	29.0 (\pm 5.78)
Alcoholic Cirrhosis (n=18)	1 g	0.85 (\pm 0.58)	22.4 (\pm 10.1)	29.8 (\pm 10.7)

Pediatric Patients

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/m² twice daily (up to a maximum of 1 g twice daily) after allogeneic kidney transplantation. The pharmacokinetic data for MPA is provided in **Table 10**.

Table 10. Mean (\pm SD) Computed Pharmacokinetic Parameters for MPA by Age and Time after Allogeneic Kidney Transplantation

Age Group	(n)	Time	T_{max} (h)	Dose Adjusted ^a C_{max} (mcg/mL)	Dose Adjusted ^a AUC ₀₋₁₂ (mcg•h/mL)
1 to less than 2 yr	(6) ^d	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to less than 6 yr	(17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to less than 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
1 to less than 2 yr	(4) ^d	Late (Month 3)	0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to less than 6 yr	(15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to less than 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
1 to less than 2 yr	(4) ^d	Late (Month 9)	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to less than 6 yr	(12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to less than 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/m²

^b n=20

^c n=16

^d a subset of 1 to <6 yr

The CELLCEPT oral suspension dose of 600 mg/m² twice daily (up to a maximum of 1 g twice daily) achieved mean MPA AUC values in pediatric patients similar to those seen in adult kidney transplant patients receiving CELLCEPT capsules at a dose of 1 g twice daily in the early post-transplant period. There was wide variability in the data. As observed in adults, early post-transplant MPA AUC values were approximately 45% to 53% lower than those observed in the later post-transplant period (>3 months). MPA AUC values were similar in the early and late post-transplant period across the 1 to 18-year age range.

Male and Female Patients

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 (\pm SD) MPA AUC (0-12h) for males (n=79) was 32.0 (\pm 14.5) and for females (n=41) was 36.5 (\pm 18.8) mcg•h/mL while mean (\pm SD) MPA C_{max} was 9.96 (\pm 6.19) in the males and 10.6 (\pm 5.64) mcg/mL in the females. These differences are not of clinical significance.

Geriatric Patients

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in elderly transplant patients when compared to younger transplant patients.

Drug Interaction Studies

Acyclovir

Coadministration of MMF (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.

Antacids with Magnesium and Aluminum Hydroxides

Absorption of a single dose of MMF (2 g) was decreased when administered to 10 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 MMF was administered alone under fasting conditions.

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 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.

Cholestyramine

Following single-dose administration of 1.5 g MMF to 12 healthy volunteers pretreated with 4 g three times a day 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.

Cyclosporine

Cyclosporine (Sandimmune[®]) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g twice daily of MMF in 10 stable kidney transplant patients. The mean (±SD) AUC(0-12h) and C_{max} of cyclosporine after 14 days of multiple doses of MMF 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 MMF.

Cyclosporine A interferes with MPA enterohepatic recirculation. In kidney transplant patients, mean MPA exposure (AUC(0-12h)) was approximately 30-50% greater when MMF was administered without cyclosporine compared with when MMF was 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.

Drugs Affecting Glucuronidation

Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA AUC (0-∞) by 35% was observed with concomitant administration of isavuconazole).

Concomitant administration of telmisartan and CELLCEPT resulted in an approximately 30% decrease in MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and glucuronidation activity.

Ganciclovir

Following single-dose administration to 12 stable kidney transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean

(\pm SD) ganciclovir AUC and C_{\max} (n=10) were 54.3 (\pm 19.0) mcg•h/mL and 11.5 (\pm 1.8) mcg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (\pm 17.0) mcg•h/mL and 10.6 (\pm 2.0) mcg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (\pm SD) AUC and C_{\max} of MPA (n=12) after coadministration were 80.9 (\pm 21.6) mcg•h/mL and 27.8 (\pm 13.9) mcg/mL, respectively, compared to values of 80.3 (\pm 16.4) μ g•h/mL and 30.9 (\pm 11.2) mcg/mL, respectively, after administration of MMF alone.

Oral Contraceptives

A study of coadministration of CELLCEPT (1 g twice daily) 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 serum levels of LH, FSH and progesterone were not significantly affected. 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.

Sevelamer

Concomitant administration of sevelamer and MMF in adult and pediatric patients decreased the mean MPA C_{\max} and AUC (0-12h) by 36% and 26% respectively.

Antimicrobials

Antimicrobials eliminating beta-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antimicrobials) may interfere with the MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning antibiotics is as follows:

- **Trimethoprim/Sulfamethoxazole:** Following single-dose administration of MMF (1.5 g) to 12 healthy male volunteers on day 8 of a 10-day course of trimethoprim 160 mg/sulfamethoxazole 800 mg administered twice daily, no effect on the bioavailability of MPA was observed. The mean (\pm SD) AUC and C_{\max} of MPA after concomitant administration were 75.2 (\pm 19.8) mcg•h/mL and 34.0 (\pm 6.6) μ g/mL, respectively, compared to 79.2 (\pm 27.9) mcg•h/mL and 34.2 (\pm 10.7) mcg/mL, respectively, after administration of MMF alone.
- **Norfloxacin and Metronidazole:** Following single-dose administration of MMF (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 MMF alone ($p < 0.05$). The mean (\pm SD) MPA AUC(0-48h) after coadministration of MMF with norfloxacin or metronidazole separately was 48.3 (\pm 24) mcg•h/mL and 42.7 (\pm 23) mcg•h/mL, respectively, compared with 56.2 (\pm 24) mcg•h/mL after administration of MMF alone.
- **Ciprofloxacin and Amoxicillin Plus Clavulanic Acid:** A total of 64 CELLCEPT-treated kidney transplant recipients received either oral ciprofloxacin 500 mg twice daily or amoxicillin plus clavulanic acid 375 mg three times daily for 7 or at least 14 days, respectively. 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 antimicrobial therapy and ceased within 3 days of discontinuation of antibiotics.

- 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 MMF and rifampin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in mice, MMF in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.4 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, MMF in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.07 times the recommended clinical dose in kidney transplant patients and 0.05 times the recommended clinical dose in heart 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 and Precautions* (5.2)].

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

MMF 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 0.06 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.

14 CLINICAL STUDIES

14.1 Kidney Transplantation

Adults

The three *de novo* kidney transplantation studies compared two dose levels of oral CELLCEPT (1 g twice daily and 1.5 g twice daily) with azathioprine (2 studies) or placebo (1 study) to prevent acute rejection episodes. One of the two studies with azathioprine (AZA) control arm also included anti-thymocyte globulin (ATGAM®) induction therapy. The geographic location of the investigational sites of these studies are included in **Table 11**.

In all three *de novo* kidney transplantation studies, the primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation. Treatment failure was 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, 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 11**). 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 combined are summarized in **Table 11**. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination.

Table 11. Treatment Failure in De Novo Kidney Transplantation Studies

USA Study (N=499 patients)	CELLCEPT 2 g/day (n=167 patients)	CELLCEPT 3 g/day (n=166 patients)	AZA 1 to 2 mg/kg/day (n=166 patients)
	All 3 groups received anti-thymocyte globulin induction, cyclosporine and corticosteroids		
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/ Australia Study (N=503 patients)	CELLCEPT 2 g/day (n=173 patients)	CELLCEPT 3 g/day (n=164 patients)	AZA 100 to 150 mg/day (n=166 patients)
	No induction treatment administered; all 3 groups received cyclosporine and corticosteroids.		
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study (N=491 patients)	CELLCEPT 2 g/day (n=165 patients)	CELLCEPT 3 g/day (n=160 patients)	Placebo (n=166 patients)
	No induction treatment administered; all 3 groups received cyclosporine and corticosteroids.		
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

*Does not include death and graft loss as reason for early termination.

No advantage of CELLCEPT at 12 months with respect to graft loss or patient death (combined) was established (**Table 12**). 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 12. De Novo Kidney Transplantation Studies Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months

Study	CELLCEPT 2 g/day	CELLCEPT 3 g/day	Control (AZA 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- De Novo Kidney transplantation PK Study with Long Term Follow-Up

One open-label, safety and pharmacokinetic study of CELLCEPT oral suspension 600 mg/m² twice daily (up to 1 g twice daily) in combination with cyclosporine and corticosteroids was performed at centers in the United States (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 (6.1)*], and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g twice daily CELLCEPT capsules [see *Clinical Pharmacology (12.3)*]. 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 post-transplant was similar to that observed in adult kidney transplant patients.

14.2 Heart Transplantation

A double-blind, randomized, comparative, parallel-group, multicenter study in primary *de novo* heart transplant recipients was performed at centers in the United States (20), in Canada (1), in Europe (5) and in Australia (2). The total number of patients enrolled (ITT population) was 650; 72 never received study drug and 578 received study drug (Safety Population). Patients received CELLCEPT 1.5 g twice daily (n=289) or AZA 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 re-transplanted or died, within the first 6 months, and (2) the proportion of patients who died or were re-transplanted 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.

The analyses of the endpoints showed:

- Rejection: No difference was established between CELLCEPT and AZA with respect to biopsy-proven rejection with hemodynamic compromise.
- Survival: CELLCEPT was shown to be at least as effective as AZA in preventing death or re-transplantation at 1 year (see **Table 13**).

Table 13. De Novo Heart Transplantation Study Rejection at 6 Months/Death or Re-transplantation at 1 Year

	All Patients (ITT)		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 re-transplantation 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/m² or a 25% decrease; ejection fraction $\leq 30\%$; pulmonary artery oxygen saturation $\leq 60\%$ or a 25% decrease; presence of new S₃ gallop; fractional shortening was $\leq 20\%$ or a 25% decrease; inotropic support required to manage the clinical condition.

14.3 Liver Transplantation

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

In combination with corticosteroids and cyclosporine, CELLCEPT demonstrated a lower rate of acute rejection at 6 months and a similar rate of death or re-transplantation at 1 year compared to AZA (**Table 14**).

Table 14. De Novo Liver Transplantation Study Rejection at 6 Months/Death or Re-transplantation at 1 Year

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

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Handling and Disposal

Mycophenolate mofetil (MMF) has demonstrated teratogenic effects in humans [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*]. CELLCEPT tablets should not be crushed and CELLCEPT capsules should not be opened or crushed. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in CELLCEPT capsules, CELLCEPT Oral Suspension (before or after constitution), or CELLCEPT Intravenous (during or after preparation) [see *Dosage and Administration (2.6)*]. Follow applicable special handling and disposal procedures¹.

16.2 CELLCEPT (mycophenolate mofetil capsules) 250 mg

Capsules Blue-brown, two-piece hard gelatin capsules, printed in black with “CELLCEPT 250” on the blue cap and “Roche” on the brown body.
Sizes Bottle of 100.....NDC 0004-0259-01 Bottle of 500.....NDC 0004-0259-43
Storage Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

16.3 CELLCEPT (mycophenolate mofetil tablets) 500 mg

Tablets
Lavender-colored, caplet-shaped, film-coated tablets printed in black with “CELLCEPT 500” on one side and “Roche” on the other
Sizes
Bottle of 100.....NDC 0004-0260-01
Bottle of 500.....NDC 0004-0260-43
Storage and Dispensing Information:
<ul style="list-style-type: none">• Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).• Dispense in light-resistant containers, such as the manufacturer’s original containers.

16.4 CELLCEPT Oral Suspension (mycophenolate mofetil for oral suspension)

For suspension: white to off-white powder blend for constitution to a white to off-white mixed-fruit flavor suspension
225 mL bottle with bottle adapter and 2 oral dispensers NDC 0004-0261-29
Storage
<ul style="list-style-type: none">• Store dry powder at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).• Store constituted suspension at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) for up to 60 days. Storage in a refrigerator at 2°C to 8°C (36°F to 46°F) is acceptable. Do not freeze.

16.5 CELLCEPT Intravenous (mycophenolate mofetil hydrochloride for injection)

For injection: 500 mg mycophenolate mofetil as the hydrochloride salt in a 20 mL sterile vial cartons of 4 vials
Cartons of 4 vials..... NDC 0004-0298-09
Storage
<ul style="list-style-type: none">• Store powder and reconstituted infusion solution at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Information for Patients

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

17.1 Embryofetal Toxicity

Pregnancy loss and malformations

- Inform females of reproductive potential and pregnant women that use of CELLCEPT during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. Advise that they must use an acceptable form of contraception [see *Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)*].
- Encourage pregnant women to enroll in the Pregnancy Exposure Registry. This registry monitors pregnancy outcomes in women exposed to mycophenolate [see *Use in Specific Populations (8.1)*].

Contraception

- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential [see *Use in Specific Populations (8.3)*].
- Females of reproductive potential must use an acceptable form of birth control during the entire CELLCEPT therapy and for 6 weeks after stopping CELLCEPT, unless the patient chooses abstinence. CELLCEPT may reduce effectiveness of oral contraceptives. Use of additional barrier contraceptive methods is recommended [see *Use in Specific Populations (8.3)*].
- 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.
- Advise sexually active male patients and/or their partners to use effective contraception during the treatment of the male patient and for at least 90 days after cessation of treatment. This recommendation is based on findings of animal studies [see *Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

17.2 Development of Lymphoma and Other Malignancies

- Inform patients that they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression [see *Warnings and Precautions (5.2)*].
- Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use of sunscreen with high protection factor.

17.3 Increased Risk of Serious Infections

Inform patients that they are at increased risk of developing a variety of infections due to immunosuppression. Instruct them to contact their physician if they develop any of the signs and symptoms of infection explained in the Medication Guide.

17.4 Blood Dyscrasias

Inform patients that they are at increased risk for developing blood adverse effects such as anemia or low white blood cells. Advise patients to immediately contact their healthcare provider

if they experience any evidence of infection, unexpected bruising, or bleeding, or any other manifestation of bone marrow suppression [see *Warnings and Precautions (5.4)*].

17.5 Gastrointestinal Tract Complications

Inform patients that CELLCEPT can cause gastrointestinal tract complications including bleeding, intestinal perforations, and gastric or duodenal ulcers. Advise the patient to contact their healthcare provider if they have symptoms of gastrointestinal bleeding, or sudden onset or persistent abdominal pain [see *Warnings and Precautions (5.5)*].

17.6 Immunizations

Inform patients that CELLCEPT can interfere with the usual response to immunizations. Before seeking vaccines on their own, advise patients to discuss first with their physician. [see *Warnings and Precautions (5.7)*].

17.7 Administration Instructions

- Advise patients not to crush CELLCEPT tablets and not to open CELLCEPT capsules.
- Advise patients to avoid inhalation or contact of the skin or mucous membranes with the powder contained in CELLCEPT capsules and with the oral suspension. If such contact occurs, they must wash the area of contact thoroughly with soap and water. In case of ocular contact, rinse eyes with plain water.
- Advise patients to take a missed dose as soon as they remember, except if it is closer than 2 hours to the next scheduled dose; in this case they should continue to take CELLCEPT at the usual times.

17.8 Blood Donation

Advise patients not to donate blood during therapy and for at least 6 weeks following discontinuation of CELLCEPT.

17.9 Semen Donation

Advise males of childbearing potential not to donate semen during therapy and for 90 days following discontinuation of CELLCEPT.

17.10 Potential to Impair Driving and Use of Machinery

Advise patients that CELLCEPT can affect the ability to drive or operate machines. Patients should avoid driving or operating machines if they experience somnolence, confusion, dizziness, tremor or hypotension during treatment with CELLCEPT.

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