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2 **CellCept®**  
3 **(mycophenolate mofetil capsules)**  
4 **(mycophenolate mofetil tablets)**

5 **CellCept® Oral Suspension**  
6 **(mycophenolate mofetil for oral suspension)**

7 **CellCept® Intravenous**  
8 **(mycophenolate mofetil hydrochloride for injection)**

9 **Rx only**

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### **WARNING**

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**Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use CellCept. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.**

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**Female users of childbearing potential must use contraception. Use of CellCept during pregnancy is associated with increased risk of pregnancy loss and congenital malformations.**

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### **DESCRIPTION**

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

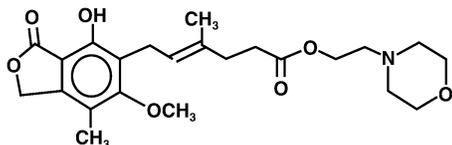
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The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of  $C_{23}H_{31}NO_7$ , a molecular weight of 433.50,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



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Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43  $\mu\text{g/mL}$  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

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

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

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

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

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

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

54 CellCept Intravenous is the hydrochloride salt of mycophenolate mofetil. The chemical  
55 name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-  
56 (1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-  
57 hexenoate hydrochloride. It has an empirical formula of  $C_{23}H_{31}NO_7$  HCl and a molecular  
58 weight of 469.96.

59 CellCept Intravenous is available as a sterile white to off-white lyophilized powder in  
60 vials containing mycophenolate mofetil hydrochloride for administration by intravenous  
61 infusion only. Each vial of CellCept Intravenous contains the equivalent of 500 mg  
62 mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate  
63 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the  
64 manufacture of CellCept Intravenous to adjust the pH. Reconstitution and dilution with  
65 5% Dextrose Injection USP yields a slightly yellow solution of mycophenolate mofetil,  
66 6 mg/mL. (For detailed method of preparation, see **DOSAGE AND**  
67 **ADMINISTRATION**).

## 68 **CLINICAL PHARMACOLOGY**

### 69 **Mechanism of Action**

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

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

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

### 97 **Pharmacokinetics**

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

### 105 **Absorption**

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

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

## 115 Distribution

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

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

## 134 Metabolism

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

144 Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to  
145 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in  
146 approximately a 40% decrease in the MPA AUC (largely as a consequence of lower  
147 concentrations in the terminal portion of the profile). These observations suggest that  
148 enterohepatic recirculation contributes to MPA plasma concentrations.

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

## 152 Excretion

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

156 recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as  
157 MPAG. At clinically encountered concentrations, MPA and MPAG are usually not  
158 removed by hemodialysis. However, at high MPAG plasma concentrations  
159 ( $>100 \mu\text{g/mL}$ ), small amounts of MPAG are removed. Bile acid sequestrants, such as  
160 cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the  
161 drug (see **OVERDOSAGE**).

162 Mean ( $\pm$ SD) apparent half-life and plasma clearance of MPA are 17.9 ( $\pm$ 6.5) hours and  
163 193 ( $\pm$ 48) mL/min following oral administration and 16.6 ( $\pm$ 5.8) hours and 177 ( $\pm$ 31)  
164 mL/min following intravenous administration, respectively.

#### 165 Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant 166 Patients

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

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

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

	Dose/Route	T <sub>max</sub> (h)	C <sub>max</sub> ( $\mu$ g/mL)	Total AUC ( $\mu$ g•h/mL)
<b>Healthy Volunteers (single dose)</b>	1 g/oral	0.80 ( $\pm$ 0.36) (n=129)	24.5 ( $\pm$ 9.5) (n=129)	63.9 ( $\pm$ 16.2) (n=117)
<b>Renal Transplant Patients (bid dosing)</b>	<b>Dose/Route</b>	<b>T<sub>max</sub> (h)</b>	<b>C<sub>max</sub> (<math>\mu</math>g/mL)</b>	<b>Interdosing Interval AUC(0-12h) (<math>\mu</math>g•h/mL)</b>
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 (<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 (<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 (>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)
<b>Cardiac Transplant Patients (bid dosing)</b>	<b>Dose/Route</b>	<b>T<sub>max</sub> (h)</b>	<b>C<sub>max</sub> (<math>\mu</math>g/mL)</b>	<b>Interdosing Interval AUC(0-12h) (<math>\mu</math>g•h/mL)</b>
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 (>6 months)	1.5 g/oral	1.1 ( $\pm$ 0.7) (n=52)	20.0 ( $\pm$ 9.4) (n=52)	54.1 <sup>a</sup> ( $\pm$ 20.4) (n=49)
<b>Hepatic Transplant Patients (bid dosing)</b>	<b>Dose/Route</b>	<b>T<sub>max</sub> (h)</b>	<b>C<sub>max</sub> (<math>\mu</math>g/mL)</b>	<b>Interdosing Interval AUC(0-12h) (<math>\mu</math>g•h/mL)</b>
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 (>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)

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<sup>a</sup>AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

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

### 189 Special Populations

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

193 **Table 2 Pharmacokinetic Parameters for MPA [mean ( $\pm$ SD)]**  
 194 **Following Single Doses of Mycophenolate Mofetil Capsules**  
 195 **in Chronic Renal and Hepatic Impairment**

<b>Renal Impairment (no. of patients)</b>	<b>Dose</b>	<b>T<sub>max</sub> (h)</b>	<b>C<sub>max</sub> (<math>\mu</math>g/mL)</b>	<b>AUC(0-96h) (<math>\mu</math>g•h/mL)</b>
Healthy Volunteers GFR >80 mL/min/1.73 m <sup>2</sup> (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 <sup>2</sup> (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 <sup>2</sup> (n=6)	1 g	0.75 ( $\pm$ 0.27)	19.0 ( $\pm$ 13.2)	52.9 ( $\pm$ 25.5)
Severe Renal Impairment GFR <25 mL/min/1.73 m <sup>2</sup> (n=7)	1 g	1.00 ( $\pm$ 0.41)	16.3 ( $\pm$ 10.8)	78.6 ( $\pm$ 46.4)
<b>Hepatic Impairment (no. of patients)</b>	<b>Dose</b>	<b>T<sub>max</sub> (h)</b>	<b>C<sub>max</sub> (<math>\mu</math>g/mL)</b>	<b>AUC(0-48h) (<math>\mu</math>g•h/mL)</b>
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)

### 196 Renal Insufficiency

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

205 Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers  
 206 (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m<sup>2</sup>) was  
 207 62.4  $\mu$ g•h/mL ( $\pm$ 19.3). Multiple dosing of mycophenolate mofetil in patients with severe  
 208 chronic renal impairment has not been studied (see **PRECAUTIONS: General** and  
 209 **DOSAGE AND ADMINISTRATION**).

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

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

221 The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis.  
222 Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG  
223 (>100 µg/mL), hemodialysis removes only small amounts of MPAG.

#### 224 Hepatic Insufficiency

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

#### 237 Pediatrics

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

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

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

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<sup>a</sup> adjusted to a dose of 600 mg/m<sup>2</sup>

<sup>b</sup> n=20

<sup>c</sup> n=16

<sup>d</sup> a subset of 1 to <6 yr

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

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### Gender

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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)  $\mu$ g•h/mL while mean ( $\pm$ SD) MPA  $C_{max}$  was 9.96 ( $\pm$ 6.19) in the males and 10.6 ( $\pm$ 5.64)  $\mu$ g/mL in the females. These differences are not of clinical significance.

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### Geriatrics

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Pharmacokinetics in the elderly have not been studied.

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## CLINICAL STUDIES

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### Adults

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The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind,

268 multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult  
269 transplant patients.

## 270 **Renal Transplant**

### 271 *Adults*

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

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

288 CellCept, in combination with corticosteroids and cyclosporine reduced (statistically  
289 significant at 0.05 level) the incidence of treatment failure within the first 6 months  
290 following transplantation. **Table 4** and **Table 5** summarize the results of these studies.  
291 These tables show (1) the proportion of patients experiencing treatment failure, (2) the  
292 proportion of patients who experienced biopsy-proven acute rejection on treatment, and  
293 (3) early termination, for any reason other than graft loss or death, without a prior biopsy-  
294 proven acute rejection episode. Patients who prematurely discontinued treatment were  
295 followed for the occurrence of death or graft loss, and the cumulative incidence of graft  
296 loss and patient death are summarized separately. Patients who prematurely discontinued  
297 treatment were not followed for the occurrence of acute rejection after termination. More  
298 patients receiving CellCept discontinued without prior biopsy-proven rejection, death or  
299 graft loss than discontinued in the control groups, with the highest rate in the CellCept  
300 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in  
301 the CellCept 3 g/day group.

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

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

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

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

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

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

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

319 *Pediatrics*

320 One open-label, safety and pharmacokinetic study of CellCept oral suspension 600  
321 mg/m<sup>2</sup> bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was  
322 performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients  
323 (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was  
324 well tolerated in pediatric patients (see **ADVERSE REACTIONS**), and the  
325 pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid  
326 CellCept capsules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). The rate  
327 of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6  
328 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6  
329 months was comparable to adults. The combined incidence of graft loss (5%) and patient  
330 death (2%) at 12 months posttransplant was similar to that observed in adult renal  
331 transplant patients.

332 **Cardiac Transplant**

333 A double-blind, randomized, comparative, parallel-group, multicenter study in primary  
334 cardiac transplant recipients was performed at 20 centers in the United States, 1 in  
335 Canada, 5 in Europe and 2 in Australia. The total number of patients enrolled was 650; 72  
336 never received study drug and 578 received study drug. Patients received CellCept 1.5 g  
337 bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with  
338 cyclosporine (Sandimmune<sup>®</sup> or Neoral<sup>®</sup>) and corticosteroids as maintenance  
339 immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion  
340 of patients who, after transplantation, had at least one endomyocardial biopsy-proven  
341 rejection with hemodynamic compromise, or were retransplanted or died, within the first  
342 6 months, and (2) the proportion of patients who died or were retransplanted during the  
343 first 12 months following transplantation. Patients who prematurely discontinued  
344 treatment were followed for the occurrence of allograft rejection for up to 6 months and  
345 for the occurrence of death for 1 year.

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

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

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

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

351 <sup>a</sup> Hemodynamic compromise occurred if any of the following criteria were met:  
352 pulmonary capillary wedge pressure  $\geq 20$  mm or a 25% increase; cardiac index  
353  $< 2.0$  L/min/m<sup>2</sup> or a 25% decrease; ejection fraction  $\leq 30\%$ ; pulmonary artery oxygen  
354 saturation  $\leq 60\%$  or a 25% decrease; presence of new S<sub>3</sub> gallop; fractional shortening  
355 was  $\leq 20\%$  or a 25% decrease; inotropic support required to manage the clinical  
356 condition.

### 357 **Hepatic Transplant**

358 A double-blind, randomized, comparative, parallel-group, multicenter study in primary  
359 hepatic transplant recipients was performed at 16 centers in the United States, 2 in  
360 Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565.  
361 Per protocol, patients received CellCept 1 g bid intravenously for up to 14 days followed  
362 by CellCept 1.5 g bid orally or azathioprine 1 to 2 mg/kg/day intravenously followed by  
363 azathioprine 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral<sup>®</sup>) and  
364 corticosteroids as maintenance immunosuppressive therapy. The actual median oral dose  
365 of azathioprine on study was 1.5 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) initially and  
366 1.26 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) at 12 months. The two primary endpoints  
367 were: (1) the proportion of patients who experienced, in the first 6 months  
368 posttransplantation, one or more episodes of biopsy-proven and treated rejection or death  
369 or retransplantation, and (2) the proportion of patients who experienced graft loss (death  
370 or retransplantation) during the first 12 months posttransplantation. Patients who  
371 prematurely discontinued treatment were followed for the occurrence of allograft  
372 rejection and for the occurrence of graft loss (death or retransplantation) for 1 year.

### 373 **Results**

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

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

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

378 **INDICATIONS AND USAGE**

379 **Renal, Cardiac, and Hepatic Transplant**

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

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

387 **CONTRAINDICATIONS**

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

392 **WARNINGS**

393 **(see boxed WARNING)**

394 Patients receiving immunosuppressive regimens involving combinations of drugs,  
 395 including CellCept, as part of an immunosuppressive regimen are at increased risk of  
 396 developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE**  
 397 **REACTIONS**). The risk appears to be related to the intensity and duration of  
 398 immunosuppression rather than to the use of any specific agent.

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

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

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

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

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

417 **Pregnancy: Teratogenic Effects: Pregnancy Category D**

418 Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant  
419 woman. Use of MMF during pregnancy is associated with an increased risk of first  
420 trimester pregnancy loss and an increased risk of congenital malformations, especially  
421 external ear and other facial abnormalities including cleft lip and palate, and anomalies of  
422 the distal limbs, heart, esophagus, and kidney. In the National Transplantation Pregnancy  
423 Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant  
424 patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of  
425 these 18 infants had structural malformations (22%). In postmarketing data (collected  
426 1995-2007) on 77 women exposed to systematic MMF during pregnancy, 25 had  
427 spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed  
428 offspring had ear abnormalities. Because these postmarketing data are reported  
429 voluntarily, it is not always possible to reliably estimate the frequency of particular  
430 adverse outcomes. These malformations seen in offspring were similar to findings in  
431 animal reproductive toxicology studies. For comparison, the background rate for  
432 congenital anomalies in the United States is about 3%, and NTPR data show a rate of  
433 4-5% among babies born to organ transplant patients using other immunosuppressive  
434 drugs.

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

442 If this drug is used during pregnancy, or if the patient becomes pregnant while taking this  
443 drug, the patient should be apprised of the potential hazard to the fetus. In certain  
444 situations, the patient and her healthcare practitioner may decide that the maternal  
445 benefits outweigh the risks to the fetus. Women using CellCept at any time during  
446 pregnancy should be encouraged to enroll in the National Transplantation Pregnancy  
447 Registry.

## 448 **Pregnancy Exposure Prevention**

449 Women of childbearing potential should have a negative serum or urine pregnancy test  
450 with a sensitivity of at least 25 mIU/mL within 1 week prior to beginning therapy.  
451 CellCept therapy should not be initiated until a negative pregnancy test report is obtained.

452 Women of childbearing potential (including pubertal girls and peri-menopausal women)  
453 taking CellCept must receive contraceptive counseling and use effective contraception.  
454 The patient should begin using her two chosen methods of contraception 4 weeks prior to  
455 starting CellCept therapy, unless abstinence is the chosen method. She should continue  
456 contraceptive use during therapy and for 6 weeks after stopping CellCept. Patients should  
457 be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill  
458 and could theoretically reduce its effectiveness (see **PRECAUTIONS: Information for**  
459 **Patients and Drug Interactions: Oral Contraceptives**).

## 460 **Neutropenia**

461 Severe neutropenia [absolute neutrophil count (ANC)  $<0.5 \times 10^3/\mu\text{L}$ ] developed in up to  
462 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients  
463 receiving CellCept 3 g daily (see **ADVERSE REACTIONS**). Patients receiving  
464 CellCept should be monitored for neutropenia (see **PRECAUTIONS: Laboratory**  
465 **Tests**). The development of neutropenia may be related to CellCept itself, concomitant  
466 medications, viral infections, or some combination of these causes. If neutropenia  
467 develops (ANC  $<1.3 \times 10^3/\mu\text{L}$ ), dosing with CellCept should be interrupted or the dose  
468 reduced, appropriate diagnostic tests performed, and the patient managed appropriately  
469 (see **DOSAGE AND ADMINISTRATION**). Neutropenia has been observed most  
470 frequently in the period from 31 to 180 days posttransplant in patients treated for  
471 prevention of renal, cardiac, and hepatic rejection.

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

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

## 477 **PRECAUTIONS**

### 478 **General**

479 Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately  
480 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with  
481 CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal  
482 bleeding (requiring hospitalization) were observed.

483 Gastrointestinal perforations have rarely been observed. Most patients receiving CellCept  
484 were also receiving other drugs known to be associated with these complications. Patients  
485 with active peptic ulcer disease were excluded from enrollment in studies with  
486 mycophenolate mofetil. Because CellCept has been associated with an increased  
487 incidence of digestive system adverse events, including infrequent cases of

488 gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be  
489 administered with caution in patients with active serious digestive system disease.

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

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

500 In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was  
501 comparable, but MPAG AUC(0-12h) was 2-fold to 3-fold higher, compared to that seen  
502 in posttransplant patients without delayed renal graft function. In the three controlled  
503 studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with  
504 delayed graft function. Although patients with delayed graft function have a higher  
505 incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than  
506 patients without delayed graft function, these events were not more frequent in patients  
507 receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for  
508 these patients; however, they should be carefully observed (see **CLINICAL**  
509 **PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

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

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

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

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

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

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

### 531 **Phenylketonurics**

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

### 535 **Information for Patients**

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

538 • Inform patients that they need repeated appropriate laboratory tests while they are  
539 taking CellCept.

540 • Inform women of childbearing potential that use of CellCept in pregnancy is  
541 associated with an increased risk of first trimester pregnancy loss and an increased  
542 risk of birth defects, and that they must use effective contraception.

543 • Discuss pregnancy plans with female patients of childbearing potential.

544 ♦ Any female of childbearing potential must use highly effective (two methods)  
545 contraception 4 weeks prior to starting CellCept therapy and continue  
546 contraception until 6 weeks after stopping CellCept treatment, unless abstinence  
547 is the chosen method (see **WARNINGS: Pregnancy**).

548 ♦ A patient who is planning a pregnancy should not use CellCept unless she cannot  
549 be successfully treated with other immunosuppressant drugs.

### 550 **Laboratory Tests**

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

### 555 **Drug Interactions**

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

### 561 **Acyclovir**

562 Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy  
563 volunteers resulted in no significant change in MPA AUC and  $C_{max}$ . However, MPAG  
564 and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because

565 MPAG plasma concentrations are increased in the presence of renal impairment, as are  
566 acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its  
567 prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the  
568 concentrations of both drugs.

#### 569 Antacids With Magnesium and Aluminum Hydroxides

570 Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when  
571 administered to ten rheumatoid arthritis patients also taking Maalox<sup>®</sup> TC (10 mL qid).  
572 The  $C_{max}$  and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when  
573 mycophenolate mofetil was administered alone under fasting conditions. CellCept may  
574 be administered to patients who are also taking antacids containing magnesium and  
575 aluminum hydroxides; however, it is recommended that CellCept and the antacid not be  
576 administered simultaneously.

#### 577 Cholestyramine

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

#### 586 Cyclosporine

587 Cyclosporine (Sandimmune<sup>®</sup>) pharmacokinetics (at doses of 275 to 415 mg/day) were  
588 unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10  
589 stable renal transplant patients. The mean ( $\pm$ SD) AUC(0-12h) and  $C_{max}$  of cyclosporine  
590 after 14 days of multiple doses of mycophenolate mofetil were 3290 ( $\pm$ 822) ng•h/mL and  
591 753 ( $\pm$ 161) ng/mL, respectively, compared to 3245 ( $\pm$ 1088) ng•h/mL and 700 ( $\pm$ 246)  
592 ng/mL, respectively, 1 week before administration of mycophenolate mofetil. The effect  
593 of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in  
594 this study; however, plasma concentrations of MPA were similar to that for healthy  
595 volunteers.

#### 596 Ganciclovir

597 Following single-dose administration to 12 stable renal transplant patients, no  
598 pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and  
599 intravenous ganciclovir (5 mg/kg). Mean ( $\pm$ SD) ganciclovir AUC and  $C_{max}$  (n=10) were  
600 54.3 ( $\pm$ 19.0)  $\mu$ g•h/mL and 11.5 ( $\pm$ 1.8)  $\mu$ g/mL, respectively, after coadministration of the  
601 two drugs, compared to 51.0 ( $\pm$ 17.0)  $\mu$ g•h/mL and 10.6 ( $\pm$ 2.0)  $\mu$ g/mL, respectively, after  
602 administration of intravenous ganciclovir alone. The mean ( $\pm$ SD) AUC and  $C_{max}$  of MPA  
603 (n=12) after coadministration were 80.9 ( $\pm$ 21.6)  $\mu$ g•h/mL and 27.8 ( $\pm$ 13.9)  $\mu$ g/mL,  
604 respectively, compared to values of 80.3 ( $\pm$ 16.4)  $\mu$ g•h/mL and 30.9 ( $\pm$ 11.2)  $\mu$ g/mL,  
605 respectively, after administration of mycophenolate mofetil alone. Because MPAG

606 plasma concentrations are increased in the presence of renal impairment, as are  
607 ganciclovir concentrations, the two drugs will compete for tubular secretion and thus  
608 further increases in concentrations of both drugs may occur. In patients with renal  
609 impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are  
610 coadministered, patients should be monitored carefully.

### 611 Oral Contraceptives

612 A study of coadministration of CellCept (1 g bid) and combined oral contraceptives  
613 containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20  
614 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18  
615 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was  
616 similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel  
617 AUC(0-24h) significantly decreased by about 15%. There was large inter-patient  
618 variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol.  
619 Mean serum levels of LH, FSH and progesterone were not significantly affected.  
620 CellCept may not have any influence on the ovulation-suppressing action of the studied  
621 oral contraceptives. However, it is recommended that oral contraceptives are  
622 coadministered with CellCept with caution and additional birth control methods be  
623 considered (see **WARNINGS: Pregnancy**).

### 624 Trimethoprim/sulfamethoxazole

625 Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy  
626 male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole  
627 800 mg administered bid, no effect on the bioavailability of MPA was observed. The  
628 mean ( $\pm$ SD) AUC and  $C_{\max}$  of MPA after concomitant administration were 75.2 ( $\pm$ 19.8)  
629  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 34.0 ( $\pm$ 6.6)  $\mu\text{g}/\text{mL}$ , respectively, compared to 79.2 ( $\pm$ 27.9)  $\mu\text{g}\cdot\text{h}/\text{mL}$  and  
630 34.2 ( $\pm$ 10.7)  $\mu\text{g}/\text{mL}$ , respectively, after administration of mycophenolate mofetil alone.

### 631 Other Interactions

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

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

### 642 Live Vaccines

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

647 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

664 Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to  
665 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal  
666 transplant patients and 0.07 times the recommended clinical dose in cardiac transplant  
667 patients when corrected for BSA. In a female fertility and reproduction study conducted  
668 in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and  
669 eyes) in the first generation offspring in the absence of maternal toxicity. This dose was  
670 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the  
671 recommended clinical dose in cardiac transplant patients when corrected for BSA. No  
672 effects on fertility or reproductive parameters were evident in the dams or in the  
673 subsequent generation.

674 **Pregnancy**

675 **Teratogenic Effects:** Pregnancy Category D. See **WARNINGS** section.

676 **Nursing Mothers**

677 Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be  
678 excreted in milk. It is not known whether this drug is excreted in human milk. Because  
679 many drugs are excreted in human milk, and because of the potential for serious adverse  
680 reactions in nursing infants from mycophenolate mofetil, a decision should be made  
681 whether to discontinue nursing or to discontinue the drug, taking into account the  
682 importance of the drug to the mother.

683 **Pediatric Use**

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

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

#### 690 **Geriatric Use**

691 Clinical studies of CellCept did not include sufficient numbers of subjects aged 65 and  
692 over to determine whether they respond differently from younger subjects. Other reported  
693 clinical experience has not identified differences in responses between the elderly and  
694 younger patients. In general dose selection for an elderly patient should be cautious,  
695 reflecting the greater frequency of decreased hepatic, renal or cardiac function and of  
696 concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse  
697 reactions compared with younger individuals (see **ADVERSE REACTIONS**).

#### 698 **ADVERSE REACTIONS**

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

#### 704 **CellCept Oral**

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

#### 709 **Geriatrics**

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

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

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**Table 8 Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥20% of Patients in the CellCept Group)**

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

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

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

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

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

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

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

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

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

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

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

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

759 All transplant patients are at increased risk of opportunistic infections. The risk increases  
760 with total immunosuppressive load (see **WARNINGS**). **Table 9** shows the incidence of  
761 opportunistic infections that occurred in the renal, cardiac, and hepatic transplant  
762 populations in the azathioprine-controlled prevention trials:

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**Table 9**      **Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection**

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

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

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

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

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

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

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**Table 10 Adverse Events Reported in 3% to <20% of Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids**

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

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

787 **Pediatrics**

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

794 **CellCept Intravenous**

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

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

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

### 807 **Postmarketing Experience**

808 *Congenital Disorders:* Congenital malformations including ear malformations have been  
809 reported in offspring of patients exposed to mycophenolate mofetil during pregnancy (see  
810 **WARNINGS: Pregnancy**).

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

813 *Resistance Mechanism Disorders:* Serious life-threatening infections such as meningitis  
814 and infectious endocarditis have been reported occasionally and there is evidence of a  
815 higher frequency of certain types of serious infections such as tuberculosis and atypical  
816 mycobacterial infection.

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

### 821 **OVERDOSAGE**

822 The experience with overdose of CellCept in humans is very limited. The events received  
823 from reports of overdose fall within the known safety profile of the drug. The highest  
824 dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited  
825 experience with cardiac and hepatic transplant patients in clinical trials, the highest doses  
826 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  
827 rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea,  
828 vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally  
829 neutropenia, leading to a need to reduce or discontinue dosing.

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

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

## 842 **DOSAGE AND ADMINISTRATION**

### 843 **Renal Transplantation**

#### 844 **Adults**

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

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

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

### 857 **Cardiac Transplantation**

#### 858 **Adults**

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

### 861 **Hepatic Transplantation**

#### 862 **Adults**

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

### 865 **CellCept Capsules, Tablets, and Oral Suspension**

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

#### 871 *Note:*

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

### 874 **Patients With Hepatic Impairment**

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

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

## 881 Geriatrics

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

## 886 Preparation of Oral Suspension

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

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

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

- 896 1. Tap the closed bottle several times to loosen the powder.
- 897 2. Measure 94 mL of water in a graduated cylinder.
- 898 3. Add approximately half the total amount of water for constitution to the bottle and  
899 shake the closed bottle well for about 1 minute.
- 900 4. Add the remainder of water and shake the closed bottle well for about 1 minute.
- 901 5. Remove the child-resistant cap and push bottle adapter into neck of bottle.
- 902 6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the  
903 bottle adapter in the bottle and child-resistant status of the cap.  
904

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

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

## 912 CellCept Intravenous

### 913 Adults

914 CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral  
915 suspension recommended for patients unable to take oral CellCept. CellCept Intravenous  
916 should be administered within 24 hours following transplantation. CellCept Intravenous

917 can be administered for up to 14 days; patients should be switched to oral CellCept as  
918 soon as they can tolerate oral medication.

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

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

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

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

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

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

#### 942 **Step 1**

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

950

#### 951 **Step 2**

- 952 a) To prepare a 1 g dose, further dilute the contents of the two reconstituted vials  
953 (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g  
954 dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL)  
955 into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions  
956 is 6 mg mycophenolate mofetil per mL.

957 b) Inspect the infusion solution for particulate matter or discoloration. Discard the  
958 infusion solution if particulate matter or discoloration is observed.  
959

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

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

### 966 **Dosage Adjustments**

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

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

976 If neutropenia develops (ANC <1.3 x 10<sup>3</sup>/μL), dosing with CellCept should be  
977 interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient  
978 managed appropriately (see **WARNINGS, ADVERSE REACTIONS,** and  
979 **PRECAUTIONS: Laboratory Tests**).

### 980 **HANDLING AND DISPOSAL**

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

992 **HOW SUPPLIED**

993 **CellCept (mycophenolate mofetil capsules) 250 mg**

994

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

997 NDC Number

Size

998 NDC 0004-0259-01

Bottle of 100

999 NDC 0004-0259-05

Package containing 12 bottles of 120

1000 NDC 0004-0259-43

Bottle of 500

1001 **Storage**

1002 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

1003 **CellCept (mycophenolate mofetil tablets) 500 mg**

1004

1005 Lavender-colored, caplet-shaped, film-coated tablets printed in black with “CellCept  
1006 500” on one side and “Roche” on the other. Supplied in the following presentations:

1007 NDC Number

Size

1008 NDC 0004-0260-01

Bottle of 100

1009 NDC 0004-0260-43

Bottle of 500

1010 **Storage and Dispensing Information**

1011 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in  
1012 light-resistant containers, such as the manufacturer’s original containers.

1013 **CellCept Oral Suspension (mycophenolate mofetil for oral suspension)**

1014 Supplied as a white to off-white powder blend for constitution to a white to off-white  
1015 mixed-fruit flavor suspension. Supplied in the following presentation:

1016 NDC Number

Size

1017 NDC 0004-0261-29

225 mL bottle with bottle adapter and 2 oral dispensers

1018 **Storage**

1019 Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

1020 Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to  
1021 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable.

1022 Do not freeze.

1023 **CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)**

1024 Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate  
1025 mofetil as the hydrochloride salt in cartons of 4 vials:

1026 NDC Number

1027 NDC 0004-0298-09

1028 **Storage**

1029 Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to  
1030 15° to 30°C (59° to 86°F).

1031

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1037

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