

- 1 **CellCept®**
2 **(mycophenolate mofetil capsules)**
3 **(mycophenolate mofetil tablets)**
4 **CellCept® Oral Suspension**
5 **(mycophenolate mofetil for oral suspension)**
6 **CellCept® Intravenous**
7 **(mycophenolate mofetil hydrochloride for injection)**
8 **Rx only**

WARNING

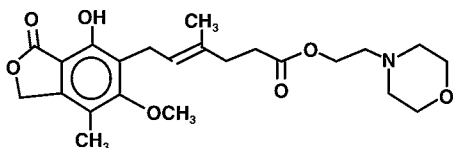
10 **Immunosuppression may lead to increased susceptibility to infection and possible**
11 **development of lymphoma. Only physicians experienced in immunosuppressive**
12 **therapy and management of renal, cardiac or hepatic transplant patients should use**
13 **CellCept. Patients receiving the drug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

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

DESCRIPTION

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

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



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29 Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in
30 water (43 $\mu\text{g/mL}$ at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH
31 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol.
32 The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The
33 pK_a values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the
34 phenolic group.

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

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

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

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

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

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

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

67 **CLINICAL PHARMACOLOGY**

68 **Mechanism of Action**

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

72 Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the
73 canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited
74 proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats,
75 as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in

76 combination with other immunosuppressive agents in these studies. Mycophenolate
77 mofetil has been demonstrated to inhibit immunologically mediated inflammatory
78 responses in animal models and to inhibit tumor development and prolong survival in
79 murine tumor transplant models.

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

96 **Pharmacokinetics**

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

104 **Absorption**

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

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

114 **Distribution**

115 The mean (\pm SD) apparent volume of distribution of MPA in 12 healthy volunteers is
116 approximately 3.6 (\pm 1.5) and 4.0 (\pm 1.2) L/kg following intravenous and oral
117 administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to

118 plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges
119 that are normally seen in stable renal transplant patients; however, at higher MPAG
120 concentrations (observed in patients with renal impairment or delayed renal graft
121 function), the binding of MPA may be reduced as a result of competition between MPAG
122 and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations
123 was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into
124 the cellular fractions of blood.

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

133 Metabolism

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

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

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

151 Excretion

152 Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally
153 administered radiolabeled mycophenolate mofetil resulted in complete recovery of the
154 administered dose, with 93% of the administered dose recovered in the urine and 6%
155 recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as
156 MPAG. At clinically encountered concentrations, MPA and MPAG are usually not
157 removed by hemodialysis. However, at high MPAG plasma concentrations
158 (>100 $\mu\text{g/mL}$), small amounts of MPAG are removed. Bile acid sequestrants, such as
159 cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the
160 drug (see **OVERDOSAGE**).

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

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

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

173 Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate
174 mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than
175 those observed after oral administration of a similar dose in the immediate posttransplant
176 phase. In hepatic transplant patients, administration of 1 g bid intravenous CellCept
177 followed by 1.5 g bid oral CellCept resulted in mean MPA AUC values similar to those
178 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 _{max} (h)	C _{max} (μ g/mL)	Total AUC (μ g•h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (\pm 0.36) (n=129)	24.5 (\pm 9.5) (n=129)	63.9 (\pm 16.2) (n=117)
Renal Transplant Patients (bid dosing)				Interdosing Interval AUC(0-12h) (μg•h/mL)
Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/mL)	
5 days	1 g/iv	1.58 (\pm 0.46) (n=31)	12.0 (\pm 3.82) (n=31)	40.8 (\pm 11.4) (n=31)
6 days	1 g/oral	1.33 (\pm 1.05) (n=31)	10.7 (\pm 4.83) (n=31)	32.9 (\pm 15.0) (n=31)
Early (<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)
Cardiac Transplant Patients (bid dosing)				Interdosing Interval AUC(0-12h) (μg•h/mL)
Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/mL)	
Early (Day before discharge)	1.5 g/oral	1.8 (\pm 1.3) (n=11)	11.5 (\pm 6.8) (n=11)	43.3 (\pm 20.8) (n=9)
Late (>6 months)	1.5 g/oral	1.1 (\pm 0.7) (n=52)	20.0 (\pm 9.4) (n=52)	54.1 ^a (\pm 20.4) (n=49)
Hepatic Transplant Patients (bid dosing)				Interdosing Interval AUC(0-12h) (μg•h/mL)
Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/mL)	
4 to 9 days	1 g/iv	1.50 (\pm 0.517) (n=22)	17.0 (\pm 12.7) (n=22)	34.0 (\pm 17.4) (n=22)
Early (5 to 8 days)	1.5 g/oral	1.15 (\pm 0.432) (n=20)	13.1 (\pm 6.76) (n=20)	29.2 (\pm 11.9) (n=20)
Late (>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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^aAUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

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

188 Special Populations

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

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

Renal Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (μg/mL)	AUC(0-96h) (μg•h/mL)
Healthy Volunteers GFR >80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	25.3 (\pm 7.99)	45.0 (\pm 22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	26.0 (\pm 3.82)	59.9 (\pm 12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	19.0 (\pm 13.2)	52.9 (\pm 25.5)
Severe Renal Impairment GFR <25 mL/min/1.73 m ² (n=7)	1 g	1.00 (\pm 0.41)	16.3 (\pm 10.8)	78.6 (\pm 46.4)
Hepatic Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (μg/mL)	AUC(0-48h) (μg•h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (\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)

195 Renal Insufficiency

196 In a single-dose study, MMF was administered as capsule or intravenous infusion over 40
 197 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic
 198 renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m²] was about 75%
 199 higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m²). In
 200 addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers
 201 with severe renal impairment than in volunteers with mild renal impairment or healthy
 202 volunteers, consistent with the known renal elimination of MPAG. No data are available
 203 on the safety of long-term exposure to this level of MPAG.

204 Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers
 205 (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) was
 206 62.4 μ g•h/mL (\pm 19.3). Multiple dosing of mycophenolate mofetil in patients with severe
 207 chronic renal impairment has not been studied (see **PRECAUTIONS: General** and
 208 **DOSAGE AND ADMINISTRATION**).

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

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

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

223 Hepatic Insufficiency

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

236 Pediatrics

237 The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric
238 patients (ranging from 1 year to 18 years of age) receiving CellCept oral suspension at a
239 dose of 600 mg/m² bid (up to a maximum of 1 g bid) after allogeneic renal
240 transplantation. The pharmacokinetic data for MPA is provided in **Table 3**:

241
242**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 ^a C_{max} (μ g/mL)	Dose Adjusted ^a AUC ₀₋₁₂ (μ g•h/mL)
1 to <2 yr	(6) ^d	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) ^b
1 to <2 yr	(4) ^d	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) ^c
1 to <2 yr	(4) ^d	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)

243 ^aadjusted to a dose of 600 mg/m²244 ^bn=20245 ^cn=16246 ^da subset of 1 to <6 yr

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248 The CellCept oral suspension dose of 600 mg/m² bid (up to a maximum of 1 g bid)
 249 achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal
 250 transplant patients receiving CellCept capsules at a dose of 1 g bid in the early
 251 posttransplant period. There was wide variability in the data. As observed in adults, early
 252 posttransplant MPA AUC values were approximately 45% to 53% lower than those
 253 observed in the later posttransplant period (>3 months). MPA AUC values were similar
 254 in the early and late posttransplant period across the 1 year to 18 year age range.

255 **Gender**

256 Data obtained from several studies were pooled to look at any gender-related differences
 257 in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (\pm SD) MPA
 258 AUC(0-12h) for males (n=79) was 32.0 (\pm 14.5) and for females (n=41) was 36.5 (\pm 18.8)
 259 μ 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)
 260 μ g/mL in the females. These differences are not of clinical significance.

261 **Geriatrics**

262 Pharmacokinetics in the elderly have not been studied.

263 **CLINICAL STUDIES**264 **Adults**

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

269 Renal Transplant**270 Adults**

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

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

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

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

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

304 ^a Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.

305 ^b Does not include death and graft loss as reason for early termination.

306 ^c MMF or azathioprine/cyclosporine/corticosteroids.

307 ^d MMF or placebo/cyclosporine/corticosteroids.

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

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

315 **Table 5 Renal Transplant Studies**
316 **Cumulative Incidence of Combined Graft Loss or Patient**
317 **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%

318 *Pediatrics*

319 One open-label, safety and pharmacokinetic study of CellCept oral suspension 600
320 mg/m² bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was
321 performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients
322 (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was
323 well tolerated in pediatric patients (see **ADVERSE REACTIONS**), and the
324 pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid
325 CellCept capsules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). The rate
326 of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6
327 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6
328 months was comparable to adults. The combined incidence of graft loss (5%) and patient
329 death (2%) at 12 months posttransplant was similar to that observed in adult renal
330 transplant patients.

331 **Cardiac Transplant**

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

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

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

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

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

350 ^a Hemodynamic compromise occurred if any of the following criteria were met:
351 pulmonary capillary wedge pressure ≥ 20 mm or a 25% increase; cardiac index
352 < 2.0 L/min/m² or a 25% decrease; ejection fraction $\leq 30\%$; pulmonary artery oxygen
353 saturation $\leq 60\%$ or a 25% decrease; presence of new S₃ gallop; fractional shortening
354 was $\leq 20\%$ or a 25% decrease; inotropic support required to manage the clinical
355 condition.

356 Hepatic Transplant

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

372 Results

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

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

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

377 **INDICATIONS AND USAGE**378 **Renal, Cardiac, and Hepatic Transplant**

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

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

386 **CONTRAINDICATIONS**

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

391 **WARNINGS**

392 (see **boxed WARNING**)

393 **Lymphoma and Malignancy**

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

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

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

407 Combination with Other Immunosuppressive Agents

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

413 Infections

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

419 Latent Viral Infections

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

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

434 BKVAN is associated with serious outcomes, including deteriorating renal function and
435 renal graft loss (see **ADVERSE REACTIONS: Postmarketing Experience**). Patient
436 monitoring may help detect patients at risk for BK virus-associated nephropathy.
437 Reduction in immunosuppression should be considered for patients who develop
438 evidence of BK virus-associated nephropathy.

439 Pregnancy: Teratogenic Effects: Pregnancy Category D

440 Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant
441 woman. Use of MMF during pregnancy is associated with an increased risk of first
442 trimester pregnancy loss and an increased risk of congenital malformations, especially
443 external ear and other facial abnormalities including cleft lip and palate, and anomalies of
444 the distal limbs, heart, esophagus, and kidney. In the National Transplantation Pregnancy
445 Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant
446 patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of
447 these 18 infants had structural malformations (22%). In postmarketing data (collected
448 1995-2007) on 77 women exposed to systemic MMF during pregnancy, 25 had

449 spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed
450 offspring had ear abnormalities. Because these postmarketing data are reported
451 voluntarily, it is not always possible to reliably estimate the frequency of particular
452 adverse outcomes. These malformations seen in offspring were similar to findings in
453 animal reproductive toxicology studies. For comparison, the background rate for
454 congenital anomalies in the United States is about 3%, and NTPR data show a rate of
455 4-5% among babies born to organ transplant patients using other immunosuppressive
456 drugs.

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

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

470 **Pregnancy Exposure Prevention**

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

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

482 **Neutropenia**

483 Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$] developed in up to
484 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients
485 receiving CellCept 3 g daily (see **ADVERSE REACTIONS**). Patients receiving
486 CellCept should be monitored for neutropenia (see **PRECAUTIONS: Laboratory**
487 **Tests**). The development of neutropenia may be related to CellCept itself, concomitant
488 medications, viral infections, or some combination of these causes. If neutropenia
489 develops (ANC $<1.3 \times 10^3/\mu\text{L}$), dosing with CellCept should be interrupted or the dose
490 reduced, appropriate diagnostic tests performed, and the patient managed appropriately
491 (see **DOSAGE AND ADMINISTRATION**). Neutropenia has been observed most

492 frequently in the period from 31 to 180 days posttransplant in patients treated for
493 prevention of renal, cardiac, and hepatic rejection.

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

497 **Pure Red Cell Aplasia (PRCA)**

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

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

507 **PRECAUTIONS**

508 **General**

509 Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately
510 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with
511 CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal
512 bleeding (requiring hospitalization) were observed.

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

520 Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) who have
521 received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative
522 to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data
523 are available on the safety of long-term exposure to these levels of MPAG. Doses of
524 CellCept greater than 1 g administered twice a day to renal transplant patients should be
525 avoided and they should be carefully observed (see **CLINICAL PHARMACOLOGY:**
526 **Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

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

530 In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was
531 comparable, but MPAG AUC(0-12h) was 2-fold to 3-fold higher, compared to that seen

532 in posttransplant patients without delayed renal graft function. In the three controlled
533 studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with
534 delayed graft function. Although patients with delayed graft function have a higher
535 incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than
536 patients without delayed graft function, these events were not more frequent in patients
537 receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for
538 these patients; however, they should be carefully observed (see **CLINICAL**
539 **PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

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

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

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

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

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

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

561 **Phenylketonurics**

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

565 **Information for Patients**

- 566 • Give patients complete dosage instructions and inform them about the increased risk
567 of lymphoproliferative disease and certain other malignancies.
- 568 • Inform patients that they need repeated appropriate laboratory tests while they are
569 taking CellCept.

- 570 • Inform women of childbearing potential that use of CellCept in pregnancy is
571 associated with an increased risk of first trimester pregnancy loss and an increased
572 risk of birth defects, and that they must use effective contraception.
- 573 • Discuss pregnancy plans with female patients of childbearing potential.
- 574 ♦ Any female of childbearing potential must use highly effective (two methods)
575 contraception 4 weeks prior to starting CellCept therapy and continue
576 contraception until 6 weeks after stopping CellCept treatment, unless abstinence
577 is the chosen method (see **WARNINGS: Pregnancy**).
- 578 ♦ A patient who is planning a pregnancy should not use CellCept unless she cannot
579 be successfully treated with other immunosuppressant drugs.

580 **Laboratory Tests**

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

585 **Drug Interactions**

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

592 **Acyclovir**

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

600 **Antacids With Magnesium and Aluminum Hydroxides**

601 Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when
602 administered to ten rheumatoid arthritis patients also taking Maalox[®] TC (10 mL qid).
603 The C_{max} and AUC(0-24h) for MPA were 33% and 17% lower, respectively, than when
604 mycophenolate mofetil was administered alone under fasting conditions. CellCept may
605 be administered to patients who are also taking antacids containing magnesium and
606 aluminum hydroxides; however, it is recommended that CellCept and the antacid not be
607 administered simultaneously.

608 Cholestyramine

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

617 Cyclosporine

618 Cyclosporine (Sandimmune[®]) pharmacokinetics (at doses of 275 to 415 mg/day) were
619 unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10
620 stable renal transplant patients. The mean (\pm SD) AUC(0-12h) and C_{\max} of cyclosporine
621 after 14 days of multiple doses of mycophenolate mofetil were 3290 (\pm 822) ng•h/mL and
622 753 (\pm 161) ng/mL, respectively, compared to 3245 (\pm 1088) ng•h/mL and 700 (\pm 246)
623 ng/mL, respectively, 1 week before administration of mycophenolate mofetil.

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

631 Ganciclovir

632 Following single-dose administration to 12 stable renal transplant patients, no
633 pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and
634 intravenous ganciclovir (5 mg/kg). Mean (\pm SD) ganciclovir AUC and C_{\max} (n=10) were
635 54.3 (\pm 19.0) μ g•h/mL and 11.5 (\pm 1.8) μ g/mL, respectively, after coadministration of the
636 two drugs, compared to 51.0 (\pm 17.0) μ g•h/mL and 10.6 (\pm 2.0) μ g/mL, respectively, after
637 administration of intravenous ganciclovir alone. The mean (\pm SD) AUC and C_{\max} of MPA
638 (n=12) after coadministration were 80.9 (\pm 21.6) μ g•h/mL and 27.8 (\pm 13.9) μ g/mL,
639 respectively, compared to values of 80.3 (\pm 16.4) μ g•h/mL and 30.9 (\pm 11.2) μ g/mL,
640 respectively, after administration of mycophenolate mofetil alone. Because MPAG
641 plasma concentrations are increased in the presence of renal impairment, as are
642 ganciclovir concentrations, the two drugs will compete for tubular secretion and thus
643 further increases in concentrations of both drugs may occur. In patients with renal
644 impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are
645 coadministered, patients should be monitored carefully.

646 Oral Contraceptives

647 A study of coadministration of CellCept (1 g bid) and combined oral contraceptives
648 containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20
649 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18

650 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was
651 similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel
652 AUC(0-24h) significantly decreased by about 15%. There was large inter-patient
653 variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol.
654 Mean serum levels of LH, FSH and progesterone were not significantly affected.
655 CellCept may not have any influence on the ovulation-suppressing action of the studied
656 oral contraceptives. However, it is recommended that oral contraceptives are
657 coadministered with CellCept with caution and additional birth control methods be
658 considered (see **WARNINGS: Pregnancy**).

659 Sevelamer

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

667 Trimethoprim/sulfamethoxazole

668 Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy
669 male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole
670 800 mg administered bid, no effect on the bioavailability of MPA was observed. The
671 mean (\pm SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (\pm 19.8)
672 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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
673 34.2 (\pm 10.7) $\mu\text{g}/\text{mL}$, respectively, after administration of mycophenolate mofetil alone.

674 Norfloxacin and Metronidazole

675 Following single-dose administration of mycophenolate mofetil (1 g) to 11 healthy
676 volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole,
677 the mean MPA AUC_{0-48h} was significantly reduced by 33% compared to the
678 administration of mycophenolate mofetil alone ($p < 0.05$). Therefore, CellCept is not
679 recommended to be given with the combination of norfloxacin and metronidazole. There
680 was no significant effect on mean MPA AUC_{0-48h} when mycophenolate mofetil was
681 concomitantly administered with norfloxacin or metronidazole separately. The mean
682 (\pm SD) MPA AUC_{0-48h} after coadministration of mycophenolate mofetil with norfloxacin
683 or metronidazole separately was 48.3 (\pm 24) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 42.7 (\pm 23) $\mu\text{g}\cdot\text{h}/\text{mL}$,
684 respectively, compared with 56.2 (\pm 24) $\mu\text{g}\cdot\text{h}/\text{mL}$ after administration of mycophenolate
685 mofetil alone.

686 Ciprofloxacin and Amoxicillin plus Clavulanic Acid

687 A total of 64 CellCept-treated renal transplant recipients received either oral
688 ciprofloxacin 500 mg bid or amoxicillin plus clavulanic acid 375 mg tid for 7 or at least
689 14 days. Approximately 50% reductions in median trough MPA concentrations (pre-
690 dose) from baseline (CellCept alone) were observed in 3 days following commencement
691 of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA
692 concentrations tended to diminish within 14 days of antibiotic therapy and ceased within

693 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction
694 is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading
695 to a decrease in enterohepatic recirculation of MPA. The change in trough level may not
696 accurately represent changes in overall MPA exposure; therefore, clinical relevance of
697 these observations is unclear.

698 Rifampin

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

703 Other Interactions

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

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

714 Live Vaccines

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

719 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

731 The genotoxic potential of mycophenolate mofetil was determined in five assays.
732 Mycophenolate mofetil was genotoxic in the mouse lymphoma/thymidine kinase assay
733 and the in vivo mouse micronucleus assay. Mycophenolate mofetil was not genotoxic in

734 the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese
735 hamster ovary cell chromosomal aberration assay.

736 Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to
737 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal
738 transplant patients and 0.07 times the recommended clinical dose in cardiac transplant
739 patients when corrected for BSA. In a female fertility and reproduction study conducted
740 in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and
741 eyes) in the first generation offspring in the absence of maternal toxicity. This dose was
742 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the
743 recommended clinical dose in cardiac transplant patients when corrected for BSA. No
744 effects on fertility or reproductive parameters were evident in the dams or in the
745 subsequent generation.

746 **Pregnancy**

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

748 **Nursing Mothers**

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

755 **Pediatric Use**

756 Based on pharmacokinetic and safety data in pediatric patients after renal transplantation,
757 the recommended dose of CellCept oral suspension is 600 mg/m² bid (up to a maximum
758 of 1 g bid). Also see **CLINICAL PHARMACOLOGY, CLINICAL STUDIES,**
759 **ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION.**

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

762 **Geriatric Use**

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

770 **ADVERSE REACTIONS**

771 The principal adverse reactions associated with the administration of CellCept include
772 diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of
773 certain types of infections eg, opportunistic infection (see **WARNINGS: Infections** and
774 **WARNINGS: Latent Viral Infections**). The adverse event profile associated with the

775 administration of CellCept Intravenous has been shown to be similar to that observed
 776 after administration of oral dosage forms of CellCept.

777 **CellCept Oral**

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

782 **Geriatrics**

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

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

793 **Table 8 Adverse Events in Controlled Studies in Prevention of**
 794 **Renal, Cardiac or Hepatic Allograft Rejection (Reported in**
 795 **≥20% of Patients in the CellCept Group)**

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	CellCept 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336)	(n=330)	(n=326)	(n=289)	(n=289)	(n=277)	(n=287)
	%	%	%	%	%	%	%
Body as a Whole							
Pain	33.0	31.2	32.2	75.8	74.7	74.0	77.7
Abdominal pain	24.7	27.6	23.0	33.9	33.2	62.5	51.2
Fever	21.4	23.3	23.3	47.4	46.4	52.3	56.1
Headache	21.1	16.1	21.2	54.3	51.9	53.8	49.1
Infection	18.2	20.9	19.9	25.6	19.4	27.1	25.1
Sepsis	–	–	–	–	–	27.4	26.5
Asthenia	–	–	–	43.3	36.3	35.4	33.8
Chest pain	–	–	–	26.3	26.0	–	–
Back pain	–	–	–	34.6	28.4	46.6	47.4
Ascites	–	–	–	–	–	24.2	22.6
Hematologic and Lymphatic							
Anemia	25.6	25.8	23.6	42.9	43.9	43.0	53.0
Leukopenia	23.2	34.5	24.8	30.4	39.1	45.8	39.0
Thrombocytopenia	–	–	–	23.5	27.0	38.3	42.2
Hypochromic anemia	–	–	–	24.6	23.5	–	–

	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) %
Leukocytosis	–	–	–	40.5	35.6	22.4	21.3
Urogenital							
Urinary tract infection	37.2	37.0	33.7	–	–	–	–
Kidney function abnormal	–	–	–	21.8	26.3	25.6	28.9
Cardiovascular							
Hypertension	32.4	28.2	32.2	77.5	72.3	62.1	59.6
Hypotension	–	–	–	32.5	36.0	–	–
Cardiovascular disorder	–	–	–	25.6	24.2	–	–
Tachycardia	–	–	–	20.1	18.0	22.0	15.7
Metabolic and Nutritional							
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
Digestive							
Diarrhea	31.0	36.1	20.9	45.3	34.3	51.3	49.8
Constipation	22.9	18.5	22.4	41.2	37.7	37.9	38.3
Nausea	19.9	23.6	24.5	54.0	54.3	54.5	51.2
Dyspepsia	–	–	–	–	–	22.4	20.9
Vomiting	–	–	–	33.9	28.4	32.9	33.4
Anorexia	–	–	–	–	–	25.3	17.1
Liver function tests abnormal	–	–	–	–	–	24.9	19.2
Respiratory							
Infection	22.0	23.9	19.6	37.0	35.3	–	–
Dyspnea	–	–	–	36.7	36.3	31.0	30.3
Cough increased	–	–	–	31.1	25.6	–	–
Lung disorder	–	–	–	30.1	29.1	22.0	18.8
Sinusitis	–	–	–	26.0	19.0	–	–
Pleural effusion	–	–	–	–	–	34.3	35.9

	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) %
Skin and Appendages							
Rash	–	–	–	22.1	18.0	–	–
Nervous System							
Tremor	–	–	–	24.2	23.9	33.9	35.5
Insomnia	–	–	–	40.8	37.7	52.3	47.0
Dizziness	–	–	–	28.7	27.7	–	–
Anxiety	–	–	–	28.4	23.9	–	–
Paresthesia	–	–	–	20.8	18.0	–	–

796 The placebo-controlled renal transplant study generally showed fewer adverse events
797 occurring in $\geq 20\%$ of patients. In addition, those that occurred were not only qualitatively
798 similar to the azathioprine-controlled renal transplant studies, but also occurred at lower
799 rates, particularly for infection, leukopenia, hypertension, diarrhea and respiratory
800 infection.

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

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

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

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

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

820 Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving
821 CellCept (2 g or 3 g daily) with other immunosuppressive agents in controlled clinical
822 trials of renal, cardiac, and hepatic transplant patients followed for at least 1 year (see

823 **WARNINGS: Lymphoma and Malignancy**). Non-melanoma skin carcinomas occurred
 824 in 1.6% to 4.2% of patients, other types of malignancy in 0.7% to 2.1% of patients.
 825 Three-year safety data in renal and cardiac transplant patients did not reveal any
 826 unexpected changes in incidence of malignancy compared to the 1-year data.

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

829 Severe neutropenia (ANC <0.5 x 10³/μL) developed in up to 2.0% of renal transplant
 830 patients, up to 2.8% of cardiac transplant patients and up to 3.6% of hepatic transplant
 831 patients receiving CellCept 3 g daily (see **WARNINGS: Neutropenia**,
 832 **PRECAUTIONS: Laboratory Tests** and **DOSAGE AND ADMINISTRATION**).

833 All transplant patients are at increased risk of opportunistic infections. The risk increases
 834 with total immunosuppressive load (see **WARNINGS: Infections** and **WARNINGS:**
 835 **Latent Viral Infections**). **Table 9** shows the incidence of opportunistic infections that
 836 occurred in the renal, cardiac, and hepatic transplant populations in the azathioprine-
 837 controlled prevention trials:

838 **Table 9** **Viral and Fungal Infections in Controlled Studies in**
 839 **Prevention of Renal, Cardiac or Hepatic Transplant**
 840 **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

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

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

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

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

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

859
860
861**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
Hematologic and Lymphatic	coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased
Urogenital	acute kidney failure, albuminuria, dysuria, hydronephrosis, hematuria, impotence, kidney failure, kidney tubular necrosis, nocturia, oliguria, pain, prostatic disorder, pyelonephritis, scrotal edema, urine abnormality, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder
Cardiovascular	angina pectoris, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiovascular disorder, congestive heart failure, extrasystole, heart arrest, heart failure, hypotension, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, pulmonary hypertension, supraventricular tachycardia, supraventricular extrasystoles, syncope, tachycardia, thrombosis, vasodilatation, vasospasm, ventricular extrasystole, ventricular tachycardia, venous pressure increased
Metabolic and Nutritional	abnormal healing, acidosis, alkaline phosphatase increased, alkalosis, bilirubinemia, creatinine increased, dehydration, gamma glutamyl transpeptidase increased, generalized edema, gout, hypercalcemia, hypercholesteremia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypochloremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, hypovolemia, hypoxia, lactic dehydrogenase increased, respiratory acidosis, SGOT increased, SGPT increased, thirst, weight gain, weight loss
Digestive	anorexia, cholangitis, cholestatic jaundice, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, infection, jaundice, liver damage, liver function tests abnormal, melena, mouth ulceration, nausea and vomiting, oral moniliasis, rectal disorder, stomach ulcer, stomatitis

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

862 Pediatrics

863 The type and frequency of adverse events in a clinical study in 100 pediatric patients 3
 864 months to 18 years of age dosed with CellCept oral suspension 600 mg/m² bid (up to 1 g
 865 bid) were generally similar to those observed in adult patients dosed with CellCept
 866 capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain,
 867 sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension,
 868 leukopenia, and anemia, which were observed in a higher proportion in pediatric patients.

869 CellCept Intravenous

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

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

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

882 **Postmarketing Experience**

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

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

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

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

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

903 **OVERDOSAGE**

904 The experience with overdose of CellCept in humans is very limited. The events received
905 from reports of overdose fall within the known safety profile of the drug. The highest
906 dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited
907 experience with cardiac and hepatic transplant patients in clinical trials, the highest doses
908 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
909 rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea,
910 vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally
911 neutropenia, leading to a need to reduce or discontinue dosing.

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

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

924 **DOSAGE AND ADMINISTRATION**

925 **Renal Transplantation**

926 **Adults**

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

933 **Pediatrics (3 months to 18 years of age)**

934 The recommended dose of CellCept oral suspension is 600 mg/m² administered twice
935 daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body
936 surface area of 1.25 m² to 1.5 m² may be dosed with CellCept capsules at a dose of 750
937 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 m² may be
938 dosed with CellCept capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

939 **Cardiac Transplantation**

940 **Adults**

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

943 **Hepatic Transplantation**

944 **Adults**

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

947 **CellCept Capsules, Tablets, and Oral Suspension**

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

953 *Note:*

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

956 **Patients With Hepatic Impairment**

957 No dose adjustments are recommended for renal patients with severe hepatic
958 parenchymal disease. However, it is not known whether dose adjustments are needed for

959 hepatic disease with other etiologies (see **CLINICAL PHARMACOLOGY:**
960 **Pharmacokinetics**).

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

963 Geriatrics

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

968 Preparation of Oral Suspension

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

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

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

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

986

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

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

994 CellCept Intravenous

995 Adults

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

999 can be administered for up to 14 days; patients should be switched to oral CellCept as
1000 soon as they can tolerate oral medication.

1001 CellCept Intravenous must be reconstituted and diluted to a concentration of 6 mg/mL
1002 using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other
1003 intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be
1004 administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS
1005 by either peripheral or central vein.

1006 CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE
1007 ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION (see
1008 WARNINGS).

1009 **Preparation of Infusion Solution (6 mg/mL)**

1010 Caution should be exercised in the handling and preparation of solutions of CellCept
1011 Intravenous. Avoid direct contact of the prepared solution of CellCept Intravenous with
1012 skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water;
1013 rinse eyes with plain water (see **WARNINGS, PRECAUTIONS, ADVERSE**
1014 **REACTIONS, and HANDLING AND DISPOSAL**).

1015 CellCept Intravenous does not contain an antibacterial preservative; therefore,
1016 reconstitution and dilution of the product must be performed under aseptic conditions.
1017 Additionally, this product is sealed under vacuum and should retain a vacuum throughout
1018 its shelf life. If a lack of vacuum in the vial is noted while adding diluent, the vial should
1019 not be used.

1020 CellCept Intravenous infusion solution must be prepared in two steps: the first step is a
1021 reconstitution step with 5% Dextrose Injection USP, and the second step is a dilution step
1022 with 5% Dextrose Injection USP. A detailed description of the preparation is given
1023 below:

1024 Step 1

- 1025 a) Two (2) vials of CellCept Intravenous are used for preparing each 1 g dose, whereas
1026 three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial
1027 by injecting 14 mL of 5% Dextrose Injection USP.
1028 b) Gently shake the vial to dissolve the drug.
1029 c) Inspect the resulting slightly yellow solution for particulate matter and discoloration
1030 prior to further dilution. Discard the vials if particulate matter or discoloration is
1031 observed.
1032

1033 Step 2

- 1034 a) To prepare a 1 g dose, further dilute the contents of the two reconstituted vials
1035 (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g
1036 dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL)
1037 into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions
1038 is 6 mg mycophenolate mofetil per mL.

1039 b) Inspect the infusion solution for particulate matter or discoloration. Discard the
1040 infusion solution if particulate matter or discoloration is observed.
1041

1042 If the infusion solution is not prepared immediately prior to administration, the
1043 commencement of administration of the infusion solution should be within 4 hours from
1044 reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions
1045 permitted to 15° to 30°C (59° to 86°F).

1046 CellCept Intravenous should not be mixed or administered concurrently via the same
1047 infusion catheter with other intravenous drugs or infusion admixtures.

1048 **Dosage Adjustments**

1049 In renal transplant patients with severe chronic renal impairment (GFR <25 mL/min/1.73
1050 m²) outside the immediate posttransplant period, doses of CellCept greater than 1 g
1051 administered twice a day should be avoided. These patients should also be carefully
1052 observed. No dose adjustments are needed in renal transplant patients experiencing
1053 delayed graft function postoperatively (see **CLINICAL PHARMACOLOGY:**
1054 **Pharmacokinetics** and **PRECAUTIONS: General**).

1055 No data are available for cardiac or hepatic transplant patients with severe chronic renal
1056 impairment. CellCept may be used for cardiac or hepatic transplant patients with severe
1057 chronic renal impairment if the potential benefits outweigh the potential risks.

1058 If neutropenia develops (ANC <1.3 x 10³/μL), dosing with CellCept should be
1059 interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient
1060 managed appropriately (see **WARNINGS: Neutropenia**, **ADVERSE REACTIONS**,
1061 and **PRECAUTIONS: Laboratory Tests**).

1062 **HANDLING AND DISPOSAL**

1063 Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits (see
1064 **WARNINGS: Pregnancy**). CellCept tablets should not be crushed and CellCept
1065 capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or
1066 mucous membranes of the powder contained in CellCept capsules and CellCept Oral
1067 Suspension (before or after constitution). If such contact occurs, wash thoroughly with
1068 soap and water; rinse eyes with plain water. Should a spill occur, wipe up using paper
1069 towels wetted with water to remove spilled powder or suspension. Caution should be
1070 exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid
1071 direct contact of the prepared solution of CellCept Intravenous with skin or mucous
1072 membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with
1073 plain water.

1074 **HOW SUPPLIED**

1075 **CellCept (mycophenolate mofetil capsules) 250 mg**

1076

1077 Blue-brown, two-piece hard gelatin capsules, printed in black with “CellCept 250” on the
1078 blue cap and “Roche” on the brown body. Supplied in the following presentations:

- 1079 NDC Number Size
- 1080 NDC 0004-0259-01 Bottle of 100
- 1081 NDC 0004-0259-05 Package containing 12 bottles of 120
- 1082 NDC 0004-0259-43 Bottle of 500
- 1083 **Storage**
- 1084 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
- 1085 **CellCept (mycophenolate mofetil tablets) 500 mg**
- 1086
- 1087 Lavender-colored, caplet-shaped, film-coated tablets printed in black with “CellCept
- 1088 500” on one side and “Roche” on the other. Supplied in the following presentations:
- 1089 NDC Number Size
- 1090 NDC 0004-0260-01 Bottle of 100
- 1091 NDC 0004-0260-43 Bottle of 500
- 1092 **Storage and Dispensing Information**
- 1093 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in
- 1094 light-resistant containers, such as the manufacturer’s original containers.
- 1095 **CellCept Oral Suspension (mycophenolate mofetil for oral suspension)**
- 1096 Supplied as a white to off-white powder blend for constitution to a white to off-white
- 1097 mixed-fruit flavor suspension. Supplied in the following presentation:
- 1098 NDC Number Size
- 1099 NDC 0004-0261-29 225 mL bottle with bottle adapter and 2 oral dispensers
- 1100 **Storage**
- 1101 Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
- 1102 Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to
- 1103 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable.
- 1104 Do not freeze.
- 1105 **CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)**
- 1106 Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate
- 1107 mofetil as the hydrochloride salt in cartons of 4 vials:
- 1108 NDC Number
- 1109 NDC 0004-0298-09
- 1110 **Storage**
- 1111 Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to
- 1112 15° to 30°C (59° to 86°F).
- 1113
- 1114

1115 PI Revised: February 2010

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MEDICATION GUIDE

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CellCept® [SEL-sept]

1119

(mycophenolate mofetil capsules)

1120

(mycophenolate mofetil tablets)

1121

CellCept® Oral Suspension

1122

(mycophenolate mofetil for oral suspension)

1123

CellCept® Intravenous

1124

(mycophenolate mofetil hydrochloride for injection)

1125

Read the Medication Guide that comes with CellCept before you start taking it and each

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time you refill your prescription. There may be new information. This Medication Guide

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does not take the place of talking with your healthcare provider about your medical

1128

condition or your treatment.

1129

What is the most important information I should know about CellCept?

1130

CellCept can cause serious side effects:

1131

- **Possible loss of a pregnancy and higher risk of birth defects.** Women who take

1132

CellCept during pregnancy have a higher risk of losing a pregnancy (miscarriage)

1133

during the first 3 months (first trimester), and a higher risk that their baby will be

1134

born with birth defects

1135

If you are a female and are able to become pregnant

1136

- your healthcare provider must talk with you about effective birth control methods (contraceptive counseling)

1137

1138

- you should have a negative pregnancy test within 1 week before you start to take CellCept

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1140

- you must use 2 different types of effective birth control at the same time, for 4 weeks before you start taking CellCept, during your entire CellCept therapy and for 6 weeks after stopping CellCept, unless you choose to avoid sexual intercourse completely (abstinence). CellCept decreases blood levels of the hormones in birth control pills that you take by mouth. Birth control pills may not work as well while you take CellCept, and you could become pregnant

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If you plan to become pregnant, talk with your healthcare provider. Your healthcare provider will decide if other medicines to prevent rejection may be right for you. In certain situations, you and your healthcare provider may decide that taking CellCept is more important to your health than the possible risks to your unborn baby.

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- 1152 • **If you get pregnant while taking CellCept, do not stop taking CellCept. Call**
1153 **your healthcare provider right away.** You and your healthcare provider should
1154 report any cases of pregnancies to
1155
1156 ▪ FDA MedWatch at 1-800-FDA-1088
1157 ▪ Genentech at 1-888-835-2555
1158
1159 Talk to your healthcare provider about joining the National Transplantation
1160 Pregnancy Registry at 1-877-955-6877.
- 1161 • **Increased risk of getting serious infections.** CellCept weakens the body’s
1162 immune system and affects your ability to fight infections. Serious infections can
1163 happen with CellCept and can lead to death. Types of infections can include:
1164
1165 • **Viral infections.** Certain viruses can live in your body and cause active
1166 infections when your immune system is weak. Viral infections that can
1167 happen with CellCept include:
1168 • Shingles, other herpes infections, and cytomegalovirus (CMV).
1169 CMV can cause serious tissue and blood infections.
1170 • BK virus. BK virus can affect how your kidney works and cause
1171 your transplanted kidney to fail.
1172
1173 • **A brain infection called Progressive Multifocal Leukoencephalopathy**
1174 **(PML).** In some patients, CellCept may cause an infection of the brain
1175 that may cause death. You are at risk for this brain infection because you
1176 have a weakened immune system. You should tell your healthcare
1177 provider right away if you have any of the following symptoms:
1178 • Weakness on one side of the body
1179 • You do not care about things that you usually care about (apathy)
1180 • You are confused or have problems thinking
1181 • You can not control your muscles
1182
1183 • **Fungal infections.** Yeasts and other types of fungal infections can happen
1184 with CellCept and can cause serious tissue and blood infections (see
1185 **“What are the possible side effects of CellCept?”**)
1186
- 1187 **Call your healthcare provider right away if you have any of the following signs and**
1188 **symptoms of infection:**
- 1189 • Temperature of 100.5°F or greater
1190 • Cold symptoms, such as a runny nose or sore throat
1191 • Flu symptoms, such as an upset stomach, stomach pain, vomiting or
1192 diarrhea
1193 • Earache or headache
1194 • Pain during urination
1195 • White patches in the mouth or throat

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- Unexpected bruising or bleeding
 - Cuts, scrapes or incisions that are red, warm and oozing pus
 - **Increased risk of getting certain cancers.** People who take CellCept have a higher risk of getting lymphoma, and other cancers, especially skin cancer. Tell your healthcare provider if you have:
 - unexplained fever, prolonged tiredness, weight loss or lymph node swelling
 - a brown or black skin lesion with uneven borders, or one part of the lesion does not look like the other
 - a change in the size and color of a mole
 - a new skin lesion or bump
 - any other changes to your health

See the section **“What are the possible side effects of CellCept?”** for information about other serious side effects.

1211 **What is CellCept?**

1212 CellCept is a prescription medicine to prevent rejection (antirejection medicine) in people
1213 who have received a kidney, heart or liver transplant. Rejection is when the body’s
1214 immune system perceives the new organ as a “foreign” threat and attacks it.

1215 CellCept is used with other medicines called cyclosporine (Sandimmune[®], Gengraf[®],
1216 Neoral[®]) and corticosteroids. These medicines work together to prevent rejection to your
1217 transplanted organ.

1218 CellCept has been used safely and works in children who received a kidney transplant as
1219 it does in adults. It is not known if CellCept is safe and works in children who receive a
1220 heart or liver transplant.

1221 **Who should not take CellCept?**

1222 **Do not take CellCept if you are allergic to mycophenolate mofetil or any of the**
1223 **ingredients in CellCept.** See the end of this Medication Guide for a complete list of
1224 ingredients in CellCept.

1225 **What should I tell my healthcare provider before taking CellCept?**

1226 Tell your healthcare provider about all of your medical conditions, if you:

- 1227
- 1228
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- 1230
- 1231
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- 1234
- **have any digestive problems**, such as ulcers
 - **have Phenylketonuria (PKU).** CellCept oral suspension contains aspartame (a source of phenylalanine)
 - **have Lesch-Nyhan or Kelley-Seegmiller syndrome or another rare inherited deficiency hypoxanthine-guanine phosphoribosyl-transferase (HGPRT).** You should not take CellCept if you have one of these disorders
 - **plan to receive any vaccines. People taking CellCept should not take live vaccines.** Some vaccines may not work as well during treatment with CellCept

- 1235 • **are pregnant or are planning to become pregnant.** See “**What is the most**
 1236 **important information I should know about CellCept?**”
 1237 • **are breastfeeding.** It is not known if CellCept passes into breast milk. You and
 1238 your healthcare provider will decide if you will take CellCept or breastfeed. You
 1239 should not do both without first talking with your healthcare provider
 1240

1241 **Tell your healthcare provider about all of the medicines you are taking including**
 1242 **prescription and nonprescription medicines, vitamins and herbal supplements.**
 1243 Some medicines may affect the way CellCept works, and CellCept may affect how some
 1244 medicines work. Especially tell your healthcare provider if you take:

- 1245 • birth control pills (oral contraceptives). See “**What is the most important**
 1246 **information I should know about CellCept?**”
 1247 • sevelamer (Renagel[®], Renvela[™]). These products should be taken 2 hours after
 1248 taking CellCept
 1249 • acyclovir (Zovirax[®]), valacyclovir (Valtrex[®]), ganciclovir (CYTOVENE[®]-IV,
 1250 Vitrasert[®]), valganciclovir (VALCYTE[®])
 1251 • rifampin (Rifater[®], Rifamate[®], Rimactane[®], Rifadin[®])
 1252 • antacids that contain magnesium and aluminum (CellCept and the antacid should
 1253 not be taken at the same time)
 1254 • sulfamethoxazole/trimethoprim (BACTRIM[™], BACTRIM DS[™])
 1255 • norfloxacin (Noroxin[®]) and metronidazole (Flagyl[®], Flagyl[®] ER, Flagyl[®] IV,
 1256 Metro IV, Helidac[®], Pylera[™])
 1257 • ciprofloxacin (Cipro[®], Cipro[®] XR, Ciloxan[®], Proquin[®] XR) and amoxicillin plus
 1258 clavulanic acid (Augmentin[®], Augmentin XR[™])
 1259 • azathioprine (Azasan[®], Imuran[®])
 1260 • cholestyramine (Questran Light[®], Questran[®], Locholest Light, Locholest,
 1261 Prevalite[®])

1262 Know the medicines you take. Keep a list of them to show to your healthcare provider
 1263 and pharmacist when you get a new medicine. Do not take any new medicine without
 1264 talking with your healthcare provider.

1265 **How should I take CellCept?**

- 1266 • Take CellCept exactly as prescribed
 1267
 1268 • Do not stop taking CellCept or change the dose unless your healthcare provider
 1269 tells you to
 1270
 1271 • If you miss a dose of CellCept, or are not sure when you took your last dose, take
 1272 the regular amount of CellCept prescribed as soon as you remember. If it is time
 1273 for your next dose, skip the missed dose. Do not take 2 doses at the same time.
 1274 Call your healthcare provider if you are not sure what to do
 1275
 1276 • Take CellCept capsules, tablets and oral suspension on an empty stomach, either 1
 1277 hour before or 2 hours after a meal, unless your healthcare provider tells you

1278 otherwise. With the approval of your healthcare provider, in stable kidney
 1279 transplant patients, CellCept can be taken with food if necessary
 1280

- 1281 • Most people take CellCept by mouth either as blue and brown capsules or
 1282 lavender tablets. Some people may get CellCept soon after their transplant surgery
 1283 as an infusion into a vein
 1284
- 1285 • Do not crush CellCept tablets. Do not open or crush CellCept capsules
 1286
- 1287 • If you are not able to swallow CellCept tablets or capsules, your healthcare
 1288 provider may prescribe CellCept Oral Suspension. This is a liquid form of
 1289 CellCept. Your pharmacist will mix the medicine before giving it to you
 1290
- 1291 • Do not mix CellCept Oral Suspension with any other medicine
 1292
- 1293 • If you take too much CellCept, call your healthcare provider or the poison control
 1294 center right away
 1295

1296 **What should I avoid while taking CellCept?**

- 1297 • **Avoid pregnancy.** See **“What is the most important information I should know
 about CellCept?”**
- **Limit the amount of time you spend in sunlight.** Avoid using tanning beds or
 sunlamps. People who take CellCept have a higher risk of getting skin cancer. (See
 “What is the most important information I should know about CellCept?”) Wear
 protective clothing when you are in the sun and use a sunscreen with a high
 protection factor (SPF 30 and above). This is especially important if your skin is very
 fair or if you have a family history of skin cancer

1298

1299 **What are the possible side effects of CellCept?**

CellCept can cause serious side effects:

- 1300 • See **“What is the most important information I should know about CellCept?”**
- **Low blood cell counts.** People taking high doses of CellCept each day may have a
 decrease in blood counts, including
 - 1301 • **white blood cells, especially neutrophils.** Neutrophils fight against bacterial
 1302 infections. You have a higher chance of getting an infection when your white
 1303 blood cell count is low. This is most common from 3 months to 6 months after
 1304 your transplant
 - 1305 • **red blood cells.** Red blood cells carry oxygen to your body tissues. You have a
 1306 higher chance of getting severe anemia when your red blood cell count is low
 - 1307 • **platelets.** Platelets help with blood clotting
 1308

1309 Your healthcare provider will do blood tests before you start taking CellCept and
 1310 during treatment with CellCept to check your blood cell counts.

1311 Tell your healthcare provider right away if you have any signs of infection (see
 1312 **“What is the most important information I should know about CellCept?”**), or
 1313 any unexpected bruising or bleeding. Also, tell your healthcare provider if you have
 1314 unusual tiredness, lack of energy, dizziness or fainting.

- **Stomach problems.** Stomach and intestinal bleeding can happen in people who take high doses of CellCept. Bleeding can be severe and you may have to be hospitalized for treatment

1315

1316 **Common side effects include:**

- 1317 • diarrhea. Call your healthcare provider right away if you have diarrhea. Do not
 1318 stop taking CellCept without first talking with your healthcare provider
- 1319 • vomiting
- 1320 • pain
- 1321 • stomach area pain
- 1322 • swelling of the lower legs, ankles and feet
- 1323 • high blood pressure

1324

1325 Side effects that happen more often in children than in adults taking CellCept include:

- 1326 • stomach area pain
- 1327 • fever
- 1328 • infection
- 1329 • pain
- 1330 • blood infection (sepsis)
- 1331 • diarrhea
- 1332 • vomiting
- sore throat
- colds (respiratory tract infections)
- high blood pressure
- low white blood cell count
- low red blood cell count

1333

1334 These are not all of the possible side effects of CellCept. Tell your healthcare provider
 1335 about any side effect that bothers you or that does not go away.

1336 Call your doctor for medical advice about side effects. You may report side effects to the
 1337 FDA at 1-800-FDA-1088 or to Genentech at 1-888-835-2555.

1338 **How should I store CellCept?**

- 1339 • Store CellCept capsules and tablets at room temperature, between 59°F to 86°F (15°C
 1340 to 30°C). Keep the container closed tightly
- 1341
- 1342 • Store the prepared CellCept Oral Suspension at room temperature, between 59°F to
 1343 86°F (15°C to 30°C), for up to 60 days. You can also store CellCept Oral Suspension
 1344 in the refrigerator at 36°F to 46°F (2°C to 8°C). **Do not freeze CellCept Oral**
 1345 **Suspension**
- 1346
- 1347 • **Keep CellCept and all medicines out of the reach of children**

1348

1349 **General Information about CellCept**

1350 Medicines are sometimes prescribed for purposes other than those listed in a Medication
1351 Guide. Do not use CellCept for a condition for which it was not prescribed. Do not give
1352 CellCept to other people, even if they have the same symptoms that you have. It may
1353 harm them.

1354 This Medication Guide summarizes the most important information about CellCept. If
1355 you would like more information, talk with your doctor. You can ask your doctor or
1356 pharmacist for information about CellCept that is written for healthcare professionals. For
1357 more information, call 1-888-835-2555 or visit
1358 www.gene.com/gene/products/information/cellcept.

1359 **What are the ingredients in CellCept?**

1360 **Active Ingredient:** mycophenolate mofetil

1361 **Inactive Ingredients:**

1362 CellCept 250 mg capsules: croscarmellose sodium, magnesium stearate, povidone (K-90)
1363 and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2,
1364 gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and
1365 yellow iron oxide.

1366 CellCept 500 mg tablets: black iron oxide, croscarmellose sodium, FD&C blue #2
1367 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium
1368 stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron
1369 oxide, talc, and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol,
1370 methyl alcohol, n-butyl alcohol, propylene glycol, and shellac.

1371 CellCept Oral Suspension: aspartame, citric acid anhydrous, colloidal silicon dioxide,
1372 methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin,
1373 and xanthan gum.

1374 CellCept Intravenous: polysorbate 80, and citric acid. Sodium hydroxide may have been
1375 used in the manufacture of CellCept Intravenous to adjust the pH.

1376

1377 This Medication Guide has been approved by the US Food and Drug Administration.

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1381

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1383 For additional copies of this Medication Guide, please call 1-800-617-8191 or visit
1384 www.gene.com/gene/products/information/cellcept.
1385

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