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

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

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

9 **Rx only**

10 **WARNING**

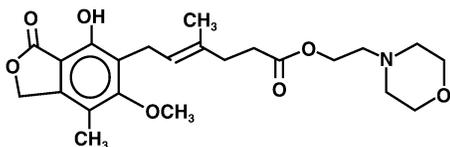
11 **Immunosuppression may lead to increased susceptibility to infection and possible**
12 **development of lymphoma. Only physicians experienced in immunosuppressive**
13 **therapy and management of renal, cardiac or hepatic transplant patients should use**
14 **CellCept. Patients receiving the drug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

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

21 **DESCRIPTION**

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

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



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

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

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

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

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

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

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

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

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

68 **CLINICAL PHARMACOLOGY**

69 **Mechanism of Action**

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

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

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

97 **Pharmacokinetics**

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

105 **Absorption**

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

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

115 Distribution

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

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

134 Metabolism

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

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

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

152 Excretion

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

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

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

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

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

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

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

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

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

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

189 Special Populations

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

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

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)

196 Renal Insufficiency

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

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

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

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

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

224 Hepatic Insufficiency

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

237 Pediatrics

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

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

Age Group	(n)	Time	T _{max} (h)	Dose Adjusted ^a C _{max} (µg/mL)	Dose Adjusted ^a AUC ₀₋₁₂ (µg•h/mL)
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)

244 ^a adjusted to a dose of 600 mg/m²

245 ^b n=20

246 ^c n=16

247 ^d a subset of 1 to <6 yr

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

256 Gender

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

262 Geriatrics

263 Pharmacokinetics in the elderly have not been studied.

264 CLINICAL STUDIES

265 Adults

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

270 **Renal Transplant**

271 *Adults*

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

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

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

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

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%

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

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

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

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

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

319 *Pediatrics*

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

332 **Cardiac Transplant**

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

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

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

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

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Biopsy-proven rejection with hemodynamic compromise at 6 months ^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%)

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

357 **Hepatic Transplant**

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

373 **Results**

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

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

	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%)

378 **INDICATIONS AND USAGE**

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

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

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

387 **CONTRAINDICATIONS**

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

392 **WARNINGS**

393 **(see boxed WARNING)**

394 **Lymphoma and Malignancy**

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

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

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

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

408 **Combination with Other Immunosuppressive Agents**

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

414 **Infections**

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

420 **Latent Viral Infections**

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

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

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

440 **Pregnancy: Teratogenic Effects: Pregnancy Category D**

441 Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant
442 woman. Use of MMF during pregnancy is associated with an increased risk of first
443 trimester pregnancy loss and an increased risk of congenital malformations, especially
444 external ear and other facial abnormalities including cleft lip and palate, and anomalies of
445 the distal limbs, heart, esophagus, and kidney. In the National Transplantation Pregnancy
446 Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant
447 patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of
448 these 18 infants had structural malformations (22%). In postmarketing data (collected
449 1995-2007) on 77 women exposed to systemic MMF during pregnancy, 25 had

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

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

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

471 **Pregnancy Exposure Prevention**

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

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

483 **Neutropenia**

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

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

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

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

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

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

508 **PRECAUTIONS**

509 **General**

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

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

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

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

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

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

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

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

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

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

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

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

562 **Phenylketonurics**

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

566 **Information for Patients**

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

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

581 **Laboratory Tests**

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

586 **Drug Interactions**

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

593 **Acyclovir**

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

601 **Antacids With Magnesium and Aluminum Hydroxides**

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

609 **Proton Pump Inhibitors (PPIs)**

610 Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy
611 volunteers and multiple doses to transplant patients receiving CellCept has been reported
612 to reduce the exposure to mycophenolic acid (MPA). An approximate reduction of 30 to
613 70% in the C_{\max} and 25% to 35% in the AUC of MPA has been observed, possibly due to
614 a decrease in MPA solubility at an increased gastric pH. The clinical impact of reduced
615 MPA exposure on organ rejection has not been established in transplant patients
616 receiving PPIs and CellCept. Because clinical relevance has not been established, PPIs
617 should be used with caution when coadministered to transplant patients being treated with
618 CellCept.

619 Cholestyramine

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

628 Cyclosporine

629 Cyclosporine (Sandimmune[®]) pharmacokinetics (at doses of 275 to 415 mg/day) were
630 unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10
631 stable renal transplant patients. The mean (\pm SD) AUC(0-12h) and C_{\max} of cyclosporine
632 after 14 days of multiple doses of mycophenolate mofetil were 3290 (\pm 822) ng•h/mL and
633 753 (\pm 161) ng/mL, respectively, compared to 3245 (\pm 1088) ng•h/mL and 700 (\pm 246)
634 ng/mL, respectively, 1 week before administration of mycophenolate mofetil.

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

642 Ganciclovir

643 Following single-dose administration to 12 stable renal transplant patients, no
644 pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and
645 intravenous ganciclovir (5 mg/kg). Mean (\pm SD) ganciclovir AUC and C_{\max} (n=10) were
646 54.3 (\pm 19.0) μ g•h/mL and 11.5 (\pm 1.8) μ g/mL, respectively, after coadministration of the
647 two drugs, compared to 51.0 (\pm 17.0) μ g•h/mL and 10.6 (\pm 2.0) μ g/mL, respectively, after
648 administration of intravenous ganciclovir alone. The mean (\pm SD) AUC and C_{\max} of MPA
649 (n=12) after coadministration were 80.9 (\pm 21.6) μ g•h/mL and 27.8 (\pm 13.9) μ g/mL,
650 respectively, compared to values of 80.3 (\pm 16.4) μ g•h/mL and 30.9 (\pm 11.2) μ g/mL,
651 respectively, after administration of mycophenolate mofetil alone. Because MPAG
652 plasma concentrations are increased in the presence of renal impairment, as are

653 ganciclovir concentrations, the two drugs will compete for tubular secretion and thus
654 further increases in concentrations of both drugs may occur. In patients with renal
655 impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are
656 coadministered, patients should be monitored carefully.

657 Oral Contraceptives

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

670 Sevelamer

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

678 Trimethoprim/sulfamethoxazole

679 Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy
680 male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole
681 800 mg administered bid, no effect on the bioavailability of MPA was observed. The
682 mean (\pm SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (\pm 19.8)
683 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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
684 34.2 (\pm 10.7) $\mu\text{g}/\text{mL}$, respectively, after administration of mycophenolate mofetil alone.

685 Norfloxacin and Metronidazole

686 Following single-dose administration of mycophenolate mofetil (1 g) to 11 healthy
687 volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole,
688 the mean MPA AUC_{0-48h} was significantly reduced by 33% compared to the
689 administration of mycophenolate mofetil alone ($p < 0.05$). Therefore, CellCept is not
690 recommended to be given with the combination of norfloxacin and metronidazole. There
691 was no significant effect on mean MPA AUC_{0-48h} when mycophenolate mofetil was
692 concomitantly administered with norfloxacin or metronidazole separately. The mean
693 (\pm SD) MPA AUC_{0-48h} after coadministration of mycophenolate mofetil with norfloxacin
694 or metronidazole separately was 48.3 (\pm 24) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 42.7 (\pm 23) $\mu\text{g}\cdot\text{h}/\text{mL}$,

695 respectively, compared with 56.2 (\pm 24) $\mu\text{g}\cdot\text{h}/\text{mL}$ after administration of mycophenolate
696 mofetil alone.

697 Ciprofloxacin and Amoxicillin plus Clavulanic Acid

698 A total of 64 CellCept-treated renal transplant recipients received either oral
699 ciprofloxacin 500 mg bid or amoxicillin plus clavulanic acid 375 mg tid for 7 or at least
700 14 days. Approximately 50% reductions in median trough MPA concentrations (pre-
701 dose) from baseline (CellCept alone) were observed in 3 days following commencement
702 of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA
703 concentrations tended to diminish within 14 days of antibiotic therapy and ceased within
704 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction
705 is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading
706 to a decrease in enterohepatic recirculation of MPA. The change in trough level may not
707 accurately represent changes in overall MPA exposure; therefore, clinical relevance of
708 these observations is unclear.

709 Rifampin

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

714 Other Interactions

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

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

725 Live Vaccines

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

730 Carcinogenesis, Mutagenesis, Impairment of Fertility

731 In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses
732 up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the
733 recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the
734 recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for
735 differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats,

736 mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest
737 dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05
738 times the recommended clinical dose in cardiac transplant patients when corrected for
739 BSA. While these animal doses were lower than those given to patients, they were
740 maximal in those species and were considered adequate to evaluate the potential for
741 human risk (see **WARNINGS**).

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

747 Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to
748 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal
749 transplant patients and 0.07 times the recommended clinical dose in cardiac transplant
750 patients when corrected for BSA. In a female fertility and reproduction study conducted
751 in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and
752 eyes) in the first generation offspring in the absence of maternal toxicity. This dose was
753 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the
754 recommended clinical dose in cardiac transplant patients when corrected for BSA. No
755 effects on fertility or reproductive parameters were evident in the dams or in the
756 subsequent generation.

757 **Pregnancy**

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

759 **Nursing Mothers**

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

766 **Pediatric Use**

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

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

773 **Geriatric Use**

774 Clinical studies of CellCept did not include sufficient numbers of subjects aged 65 and
775 over to determine whether they respond differently from younger subjects. Other reported
776 clinical experience has not identified differences in responses between the elderly and

777 younger patients. In general dose selection for an elderly patient should be cautious,
778 reflecting the greater frequency of decreased hepatic, renal or cardiac function and of
779 concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse
780 reactions compared with younger individuals (see **ADVERSE REACTIONS**).

781 **ADVERSE REACTIONS**

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

788 **CellCept Oral**

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

793 **Geriatrics**

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

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

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

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

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day	CellCept 3 g/day	Azathioprine 1.5 to 3 mg/kg/day	CellCept 3 g/day	Azathioprine 1 to 2 mg/kg/day
	(n=336) %	(n=330) %	(n=326) %	(n=289) %	(n=289) %	(n=277) %	(n=287) %
Metabolic and Nutritional							
Peripheral edema	28.6	27.0	28.2	64.0	53.3	48.4	47.7
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
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	–	–

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

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

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

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

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

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

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

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

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

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

844 All transplant patients are at increased risk of opportunistic infections. The risk increases
845 with total immunosuppressive load (see **WARNINGS: Infections** and **WARNINGS:**
846 **Latent Viral Infections**). Error! Reference source not found. **Table 9** shows the
847 incidence of opportunistic infections that occurred in the renal, cardiac, and hepatic
848 transplant populations in the azathioprine-controlled prevention trials:

849 **Table 9** **Viral and Fungal Infections in Controlled Studies in**
 850 **Prevention of Renal, Cardiac or Hepatic Transplant**
 851 **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

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

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

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

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

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

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

Body System	
Body as a Whole	abdomen enlarged, abscess, accidental injury, cellulitis, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, hernia, lab test abnormal, malaise, neck pain, pelvic pain, peritonitis
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

873 **Pediatrics**

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

880 **CellCept Intravenous**

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

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

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

893 **Postmarketing Experience**

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

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

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

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

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

914 **OVERDOSAGE**

915 The experience with overdose of CellCept in humans is very limited. The events received
916 from reports of overdose fall within the known safety profile of the drug. The highest
917 dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited
918 experience with cardiac and hepatic transplant patients in clinical trials, the highest doses
919 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
920 rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea,
921 vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally
922 neutropenia, leading to a need to reduce or discontinue dosing.

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

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

935 **DOSAGE AND ADMINISTRATION**

936 **Renal Transplantation**

937 **Adults**

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

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

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

950 **Cardiac Transplantation**

951 **Adults**

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

954 **Hepatic Transplantation**

955 **Adults**

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

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

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

964 *Note:*

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

967 **Patients With Hepatic Impairment**

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

970 hepatic disease with other etiologies (see **CLINICAL PHARMACOLOGY:**
971 **Pharmacokinetics**).

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

974 Geriatrics

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

979 **Preparation of Oral Suspension**

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

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

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

- 989 1. Tap the closed bottle several times to loosen the powder.
- 990 2. Measure 94 mL of water in a graduated cylinder.
- 991 3. Add approximately half the total amount of water for constitution to the bottle and
992 shake the closed bottle well for about 1 minute.
- 993 4. Add the remainder of water and shake the closed bottle well for about 1 minute.
- 994 5. Remove the child-resistant cap and push bottle adapter into neck of bottle.
- 995 6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the
996 bottle adapter in the bottle and child-resistant status of the cap.
- 997

998 Dispense with patient instruction sheet and oral dispensers. It is recommended to write
999 the date of expiration of the constituted suspension on the bottle label. (The shelf-life of
1000 the constituted suspension is 60 days.)

1001 After constitution the oral suspension contains 200 mg/mL mycophenolate mofetil. Store
1002 constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
1003 Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze. Discard
1004 any unused portion 60 days after constitution.

1005 **CellCept Intravenous**

1006 Adults

1007 CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral
1008 suspension recommended for patients unable to take oral CellCept. CellCept Intravenous
1009 should be administered within 24 hours following transplantation. CellCept Intravenous

1010 can be administered for up to 14 days; patients should be switched to oral CellCept as
1011 soon as they can tolerate oral medication.

1012 CellCept Intravenous must be reconstituted and diluted to a concentration of 6 mg/mL
1013 using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other
1014 intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be
1015 administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS
1016 by either peripheral or central vein.

1017 CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE
1018 ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION (see
1019 WARNINGS).

1020 **Preparation of Infusion Solution (6 mg/mL)**

1021 Caution should be exercised in the handling and preparation of solutions of CellCept
1022 Intravenous. Avoid direct contact of the prepared solution of CellCept Intravenous with
1023 skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water;
1024 rinse eyes with plain water (see **WARNINGS, PRECAUTIONS, ADVERSE**
1025 **REACTIONS, and HANDLING AND DISPOSAL**).

1026 CellCept Intravenous does not contain an antibacterial preservative; therefore,
1027 reconstitution and dilution of the product must be performed under aseptic conditions.
1028 Additionally, this product is sealed under vacuum and should retain a vacuum throughout
1029 its shelf life. If a lack of vacuum in the vial is noted while adding diluent, the vial should
1030 not be used.

1031 CellCept Intravenous infusion solution must be prepared in two steps: the first step is a
1032 reconstitution step with 5% Dextrose Injection USP, and the second step is a dilution step
1033 with 5% Dextrose Injection USP. A detailed description of the preparation is given
1034 below:

1035 Step 1

- 1036 a) Two (2) vials of CellCept Intravenous are used for preparing each 1 g dose, whereas
1037 three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial
1038 by injecting 14 mL of 5% Dextrose Injection USP.
1039 b) Gently shake the vial to dissolve the drug.
1040 c) Inspect the resulting slightly yellow solution for particulate matter and discoloration
1041 prior to further dilution. Discard the vials if particulate matter or discoloration is
1042 observed.

1043

1044 Step 2

- 1045 a) To prepare a 1 g dose, further dilute the contents of the two reconstituted vials
1046 (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g
1047 dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL)
1048 into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions
1049 is 6 mg mycophenolate mofetil per mL.

1050 b) Inspect the infusion solution for particulate matter or discoloration. Discard the
1051 infusion solution if particulate matter or discoloration is observed.
1052

1053 If the infusion solution is not prepared immediately prior to administration, the
1054 commencement of administration of the infusion solution should be within 4 hours from
1055 reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions
1056 permitted to 15° to 30°C (59° to 86°F).

1057 CellCept Intravenous should not be mixed or administered concurrently via the same
1058 infusion catheter with other intravenous drugs or infusion admixtures.

1059 **Dosage Adjustments**

1060 In renal transplant patients with severe chronic renal impairment (GFR <25 mL/min/1.73
1061 m²) outside the immediate posttransplant period, doses of CellCept greater than 1 g
1062 administered twice a day should be avoided. These patients should also be carefully
1063 observed. No dose adjustments are needed in renal transplant patients experiencing
1064 delayed graft function postoperatively (see **CLINICAL PHARMACOLOGY:**
1065 **Pharmacokinetics** and **PRECAUTIONS: General**).

1066 No data are available for cardiac or hepatic transplant patients with severe chronic renal
1067 impairment. CellCept may be used for cardiac or hepatic transplant patients with severe
1068 chronic renal impairment if the potential benefits outweigh the potential risks.

1069 If neutropenia develops (ANC <1.3 x 10³/μL), dosing with CellCept should be
1070 interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient
1071 managed appropriately (see **WARNINGS: Neutropenia**, **ADVERSE REACTIONS**,
1072 and **PRECAUTIONS: Laboratory Tests**).

1073 **HANDLING AND DISPOSAL**

1074 Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits (see
1075 **WARNINGS: Pregnancy**). CellCept tablets should not be crushed and CellCept
1076 capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or
1077 mucous membranes of the powder contained in CellCept capsules and CellCept Oral
1078 Suspension (before or after constitution). If such contact occurs, wash thoroughly with
1079 soap and water; rinse eyes with plain water. Should a spill occur, wipe up using paper
1080 towels wetted with water to remove spilled powder or suspension. Caution should be
1081 exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid
1082 direct contact of the prepared solution of CellCept Intravenous with skin or mucous
1083 membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with
1084 plain water.

1085 **HOW SUPPLIED**

1086 **CellCept (mycophenolate mofetil capsules) 250 mg**

1087

1088 Blue-brown, two-piece hard gelatin capsules, printed in black with “CellCept 250” on the
1089 blue cap and “Roche” on the brown body. Supplied in the following presentations:

