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

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

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

9 **Rx only**

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WARNING

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

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DESCRIPTION

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

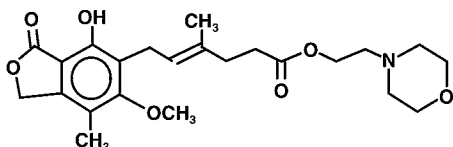
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The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and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



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

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

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

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

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

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

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

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

65 **CLINICAL PHARMACOLOGY**

66 **Mechanism of Action**

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

70 Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the
71 canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited
72 proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats,
73 as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in
74 combination with other immunosuppressive agents in these studies. Mycophenolate
75 mofetil has been demonstrated to inhibit immunologically mediated inflammatory

76 responses in animal models and to inhibit tumor development and prolong survival in
77 murine tumor transplant models.

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

94 **Pharmacokinetics**

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

102 **Absorption**

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

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

112 **Distribution**

113 The mean (\pm SD) apparent volume of distribution of MPA in 12 healthy volunteers is
114 approximately 3.6 (\pm 1.5) and 4.0 (\pm 1.2) L/kg following intravenous and oral
115 administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to
116 plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges

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

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

131 Metabolism

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

141 Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to
142 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in
143 approximately a 40% decrease in the MPA AUC (largely as a consequence of lower
144 concentrations in the terminal portion of the profile). These observations suggest that
145 enterohepatic recirculation contributes to MPA plasma concentrations.

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

149 Excretion

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

159 Mean (\pm SD) apparent half-life and plasma clearance of MPA are 17.9 (\pm 6.5) hours and
160 193 (\pm 48) mL/min following oral administration and 16.6 (\pm 5.8) hours and 177 (\pm 31)
161 mL/min following intravenous administration, respectively.

162 Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant 163 Patients

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

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

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

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

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

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

186 Special Populations

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

190 **Table 2 Pharmacokinetic Parameters for MPA [mean (\pm SD)]**
 191 **Following Single Doses of Mycophenolate Mofetil Capsules**
 192 **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)

193 Renal Insufficiency

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

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

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

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

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

221 Hepatic Insufficiency

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

234 Pediatrics

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

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

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

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^a adjusted to a dose of 600 mg/m²

^b n=20

^c n=16

^d a subset of 1 to <6 yr

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

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Gender

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

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Geriatrics

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Pharmacokinetics in the elderly have not been studied.

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CLINICAL STUDIES

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Adults

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

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

267 Renal Transplant:

268 *Adults*

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

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

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

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

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

316 *Pediatrics*

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

329 **Cardiac Transplant**

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

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

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

347 **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%)

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

354 **Hepatic Transplant**

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

370 **Results**

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

374 **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%)

375 **INDICATIONS AND USAGE**

376 **Renal, Cardiac, and Hepatic Transplant**

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

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

384 **CONTRAINDICATIONS**

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

389 **WARNINGS**

390 **(see boxed WARNING)**

391 Patients receiving immunosuppressive regimens involving combinations of drugs,
 392 including CellCept, as part of an immunosuppressive regimen are at increased risk of
 393 developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE**
 394 **REACTIONS**). The risk appears to be related to the intensity and duration of
 395 immunosuppression rather than to the use of any specific agent. Oversuppression of the
 396 immune system can also increase susceptibility to infection, including opportunistic
 397 infections, fatal infections, and sepsis.

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

401 CellCept has been administered in combination with the following agents in clinical
 402 trials: antithymocyte globulin (ATGAM[®]), OKT3 (Orthoclone OKT[®] 3), cyclosporine
 403 (Sandimmune[®], Neoral[®]) and corticosteroids. The efficacy and safety of the use of

404 CellCept in combination with other immunosuppressive agents have not been
405 determined.

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

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

411 Adverse effects on fetal development (including malformations) occurred when pregnant
412 rats and rabbits were dosed during organogenesis. These responses occurred at doses
413 lower than those associated with maternal toxicity, and at doses below the recommended
414 clinical dose for renal, cardiac or hepatic transplantation. There are no adequate and well-
415 controlled studies in pregnant women. However, as CellCept has been shown to have
416 teratogenic effects in animals, it may cause fetal harm when administered to a pregnant
417 woman. Therefore, CellCept should not be used in pregnant women unless the potential
418 benefit justifies the potential risk to the fetus.

419 Women of childbearing potential should have a negative serum or urine pregnancy test
420 with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is
421 recommended that CellCept therapy should not be initiated by the physician until a report
422 of a negative pregnancy test has been obtained.

423 Effective contraception must be used before beginning CellCept therapy, during therapy,
424 and for 6 weeks following discontinuation of therapy, even where there has been a
425 history of infertility, unless due to hysterectomy. Two reliable forms of contraception
426 must be used simultaneously unless abstinence is the chosen method (see
427 **PRECAUTIONS: Drug Interactions**). If pregnancy does occur during treatment, the
428 physician and patient should discuss the desirability of continuing the pregnancy (see
429 **PRECAUTIONS: Pregnancy and Information for Patients**).

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

433 Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$] developed in up to
434 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients
435 receiving CellCept 3 g daily (see **ADVERSE REACTIONS**). Patients receiving
436 CellCept should be monitored for neutropenia (see **PRECAUTIONS: Laboratory**
437 **Tests**). The development of neutropenia may be related to CellCept itself, concomitant
438 medications, viral infections, or some combination of these causes. If neutropenia
439 develops (ANC $<1.3 \times 10^3/\mu\text{L}$), dosing with CellCept should be interrupted or the dose
440 reduced, appropriate diagnostic tests performed, and the patient managed appropriately
441 (see **DOSAGE AND ADMINISTRATION**). Neutropenia has been observed most
442 frequently in the period from 31 to 180 days posttransplant in patients treated for
443 prevention of renal, cardiac, and hepatic rejection.

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

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

449 **PRECAUTIONS**

450 **General**

451 Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately
452 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with
453 CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal
454 bleeding (requiring hospitalization) were observed.

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

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

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

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

482 In cardiac transplant patients, the overall incidence of opportunistic infections was
483 approximately 10% higher in patients treated with CellCept than in those receiving

484 azathioprine therapy, but this difference was not associated with excess mortality due to
485 infection/sepsis among patients treated with CellCept (see **ADVERSE REACTIONS**).

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

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

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

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

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

503 **Phenylketonurics**

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

507 **Information for Patients**

508 Patients should be informed of the need for repeated appropriate laboratory tests while
509 they are receiving CellCept. Patients should be given complete dosage instructions and
510 informed of the increased risk of lymphoproliferative disease and certain other
511 malignancies. Women of childbearing potential should be instructed of the potential risks
512 during pregnancy, and that they should use effective contraception before beginning
513 CellCept therapy, during therapy, and for 6 weeks after CellCept has been stopped (see
514 **WARNINGS** and **PRECAUTIONS: Pregnancy**).

515 **Laboratory Tests**

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

520 **Drug Interactions**

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

526 **Acyclovir**

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

534 **Antacids With Magnesium and Aluminum Hydroxides**

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

542 **Cholestyramine**

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

551 **Cyclosporine**

552 Cyclosporine (Sandimmune[®]) pharmacokinetics (at doses of 275 to 415 mg/day) were
553 unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in 10
554 stable renal transplant patients. The mean (\pm SD) AUC(0-12h) and C_{max} of cyclosporine
555 after 14 days of multiple doses of mycophenolate mofetil were 3290 (\pm 822) ng•h/mL and
556 753 (\pm 161) ng/mL, respectively, compared to 3245 (\pm 1088) ng•h/mL and 700 (\pm 246)
557 ng/mL, respectively, 1 week before administration of mycophenolate mofetil. The effect
558 of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in
559 this study; however, plasma concentrations of MPA were similar to that for healthy
560 volunteers.

561 Ganciclovir

562 Following single-dose administration to 12 stable renal transplant patients, no
563 pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and
564 intravenous ganciclovir (5 mg/kg). Mean (\pm SD) ganciclovir AUC and C_{\max} (n=10) were
565 54.3 (\pm 19.0) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 11.5 (\pm 1.8) $\mu\text{g}/\text{mL}$, respectively, after coadministration of the
566 two drugs, compared to 51.0 (\pm 17.0) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 10.6 (\pm 2.0) $\mu\text{g}/\text{mL}$, respectively, after
567 administration of intravenous ganciclovir alone. The mean (\pm SD) AUC and C_{\max} of MPA
568 (n=12) after coadministration were 80.9 (\pm 21.6) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 27.8 (\pm 13.9) $\mu\text{g}/\text{mL}$,
569 respectively, compared to values of 80.3 (\pm 16.4) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 30.9 (\pm 11.2) $\mu\text{g}/\text{mL}$,
570 respectively, after administration of mycophenolate mofetil alone. Because MPAG
571 plasma concentrations are increased in the presence of renal impairment, as are
572 ganciclovir concentrations, the two drugs will compete for tubular secretion and thus
573 further increases in concentrations of both drugs may occur. In patients with renal
574 impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are
575 coadministered, patients should be monitored carefully.

576 Oral Contraceptives

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

589 Trimethoprim/sulfamethoxazole

590 Following single-dose administration of mycophenolate mofetil (1.5 g) to 12 healthy
591 male volunteers on day 8 of a 10 day course of trimethoprim 160 mg/sulfamethoxazole
592 800 mg administered bid, no effect on the bioavailability of MPA was observed. The
593 mean (\pm SD) AUC and C_{\max} of MPA after concomitant administration were 75.2 (\pm 19.8)
594 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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
595 34.2 (\pm 10.7) $\mu\text{g}/\text{mL}$, respectively, after administration of mycophenolate mofetil alone.

596 Other Interactions

597 The measured value for renal clearance of MPAG indicates removal occurs by renal
598 tubular secretion as well as glomerular filtration. Consistent with this, coadministration of
599 probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in
600 monkeys results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in
601 plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may

602 compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug
603 undergoing tubular secretion.

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

607 Live Vaccines

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

612 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

629 Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to
630 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal
631 transplant patients and 0.07 times the recommended clinical dose in cardiac transplant
632 patients when corrected for BSA. In a female fertility and reproduction study conducted
633 in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and
634 eyes) in the first generation offspring in the absence of maternal toxicity. This dose was
635 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the
636 recommended clinical dose in cardiac transplant patients when corrected for BSA. No
637 effects on fertility or reproductive parameters were evident in the dams or in the
638 subsequent generation.

639 **Pregnancy**

640 *Category C*

641 In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in
642 rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity.
643 These levels are equivalent to 0.03 to 0.92 times the recommended clinical dose in renal
644 transplant patients and 0.02 to 0.61 times the recommended clinical dose in cardiac
645 transplant patients on a BSA basis. In a female fertility and reproduction study conducted
646 in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and
647 eyes) in the first generation offspring in the absence of maternal toxicity. This dose was
648 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the
649 recommended clinical dose in cardiac transplant patients when corrected for BSA.

650 There are no adequate and well-controlled studies in pregnant women. CellCept should
651 not be used in pregnant women unless the potential benefit justifies the potential risk to
652 the fetus. Effective contraception must be used before beginning CellCept therapy, during
653 therapy and for 6 weeks after CellCept has been stopped (see **WARNINGS** and
654 **PRECAUTIONS: Information for Patients**).

655 **Nursing Mothers**

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

662 **Pediatric Use**

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

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

669 **Geriatric Use**

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

677 **ADVERSE REACTIONS**

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

683 **CellCept Oral**

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

688 **Geriatrics**

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

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

699 **Table 8 Adverse Events in Controlled Studies in Prevention of**
 700 **Renal, Cardiac or Hepatic Allograft Rejection (Reported in**
 701 **$\geq 20\%$ 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

	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) %
Hemic 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
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	–	–

	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)
	%	%	%	%	%	%	%
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	–	–

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

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

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

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

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

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

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

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

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

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

742 **Table 9** **Viral and Fungal Infections in Controlled Studies in**
 743 **Prevention of Renal, Cardiac or Hepatic Transplant**
 744 **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

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

749 In the placebo-controlled renal transplant study, the same pattern of opportunistic
 750 infection was observed compared to the azathioprine-controlled renal studies, with a

751 notably lower incidence of the following: Herpes simplex and CMV tissue-invasive
752 disease.

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

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

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

763
764
765

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

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

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

766 **Pediatrics**

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

773 **CellCept Intravenous**

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

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

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

786 **Postmarketing Experience**

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

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

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

797 **OVERDOSAGE**

798 The experience with overdose of CellCept in humans is very limited. The events received
799 from reports of overdose fall within the known safety profile of the drug. The highest
800 dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited
801 experience with cardiac and hepatic transplant patients in clinical trials, the highest doses
802 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
803 rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea,
804 vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally
805 neutropenia, leading to a need to reduce or discontinue dosing.

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

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

818 **DOSAGE AND ADMINISTRATION**

819 **Renal Transplantation**

820 **Adults**

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

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

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

833 **Cardiac Transplantation**

834 **Adults**

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

837 **Hepatic Transplantation**

838 **Adults**

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

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

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

847 *Note:*

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

850 **Patients With Hepatic Impairment**

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

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

857 Geriatrics

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

862 Preparation of Oral Suspension

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

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

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

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

880

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

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

888 CellCept Intravenous

889 Adults

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

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

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

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

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

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

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

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

918 **Step 1**

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

926

927 **Step 2**

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

933 b) Inspect the infusion solution for particulate matter or discoloration. Discard the
934 infusion solution if particulate matter or discoloration is observed.
935

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

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

942 **Dosage Adjustments**

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

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

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

956 **HANDLING AND DISPOSAL**

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

968 **HOW SUPPLIED**

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

970

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

973	<u>NDC Number</u>	<u>Size</u>
974	NDC 0004-0259-01	Bottle of 100
975	NDC 0004-0259-05	Package containing 12 bottles of 120
976	NDC 0004-0259-43	Bottle of 500

977 **Storage**

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

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

980

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

983	<u>NDC Number</u>	<u>Size</u>
984	NDC 0004-0260-01	Bottle of 100
985	NDC 0004-0260-43	Bottle of 500

986 **Storage and Dispensing Information**

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

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

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

992	<u>NDC Number</u>	<u>Size</u>
993	NDC 0004-0261-29	225 mL bottle with bottle adapter and 2 oral dispensers

994 **Storage**

995 Store dry powder at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
996 Store constituted suspension at 25°C (77°F); excursions permitted to 15° to 30°C (59° to
997 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable.
998 Do not freeze.

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

1000 Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate
1001 mofetil as the hydrochloride salt in cartons of 4 vials:

1002 NDC Number

1003 NDC 0004-0298-09

1004 **Storage**

1005 Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to
1006 15° to 30°C (59° to 86°F).

1007

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