

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-004

50-723/S-003

50-758/S-003

50-759/S-004

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: ~~50-722~~/SLR-004

Submission Dates: 8/16/1999,
10/12/1999,6/6/2000

50-723/S-003

50-758/S-003

50-759/S-004

Generic Name: Mycophenolate Mofetil

Brand Name: Cellcept®

Applicant: Roche

Final Review Date: 7/19/2000

Type of Submission: Labeling Supplement

Reviewer: Kofi A. Kumi, Ph.D.

Background

The applicant submitted supplemental labeling revision for NDA 50,722 (Cellcept® capsules) with cross-reference to NDA 50,723 (Cellcept® tablets), 50,758 (Cellcept® IV) and 50,759 (Cellcept® Suspension). The pharmacokinetic section of the application contained original reports of drug-drug interaction studies between mycophenolate mofetil (MMF) and tacrolimus (FK506, Prograf®), revised reports submitted to the above NDAs and some literature information in support of the proposed changes of the label. A review of the original reports is provided in the appendix which is on file in the Division of Pharmaceutical Evaluation III. The following is the reviewer's comments and recommendations for the proposed labeling changes in the clinical pharmacology and biopharmaceutics sections submitted by the applicant.

Recommended Labeling Changes in the Clinical Pharmacology and Biopharmaceutics Sections

(Sponsor's additions are double underline, deletions are strikeouts and reviewer's recommendations are in italics. The label referenced is the annotated label submitted on 8/16/99)

Sponsor's Proposal (Page 3, last paragraph):

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

Reviewer Comment: The deletion is not acceptable and should remain. Effect of food and recommendation for dosing with regard to food are provided in the Dosage and Administration section, hence a reference to that section is needed.

Sponsor's Proposal (Page 4, 3rd paragraph):

Metabolism: Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to — MPA via enterohepatic recirculation. [1] The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Reviewer's Comment: The addition is acceptable except the word — ' should be deleted. MPA binds to plasma protein including what is obtained via recirculation. The addition should read " In vivo, MPAG is converted to MPA via enterohepatic recirculation"

Sponsor's Proposal (page 5, 1st paragraph) :

Excretion: Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see OVERDOSAGE). [2,3,4]

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

Reviewer's Comments: The changes are acceptable

Sponsor's Proposal (Page 8 3rd and 4th paragraphs):

In patients with delayed renal graft function posttransplant, mean MPA AUC₀₋₁₂ was comparable to that seen in posttransplant patients without delayed graft function.

Mean plasma MPAG AUC₀₋₁₂ was 2-fold to 3-fold higher than in posttransplant patients without delayed graft function (see PRECAUTIONS: *General and DOSAGE AND ADMINISTRATION*).

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

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Reviewer's Comments: Paragraph 3: The following is the recommended sentence for the proposed addition "There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed graft function. However, dose adjustment does not appear to be necessary in patients with delayed graft function"

Paragraph 4: In 8 patients with primary non-function of the organ following renal transplantation, plasma concentrations of MPAG accumulated about 6 to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1 to 2-fold.

Sponsor's Proposal (Page 8, 6th paragraph)

Hepatic Insufficiency: In a single-dose (1 g, oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, [5,6] may show a different effect. In a single-dose (1 g) intravenous study of 6 volunteers with _____ alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 µg·h/mL (±15.5).

Reviewer's comments: The basis of this request is based on study CPP/MYC030/GER submitted originally to NDA 50,722 and reviewed by Dr. Chandra Sahajwalla. The changes are acceptable except how severe hepatic impairment is determined should be added. The following is recommended:

".....severe hepatic impairment (aminopyrine breath test less than 0.2% of dose)..."

Sponsor's Proposal:

Geriatric Use: Pharmacokinetics in the elderly have not been studied.

Reviewer's comment: Addition acceptable except delete the word ~~The following~~ is recommended:

"Pharmacokinetics in the elderly have not been studied"

Sponsor's Proposal (page 18, 1st paragraph)

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

Reviewer's comments: The recommendation is acceptable

Sponsor's Proposal

Oral Contraceptives:

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Reviewer's comments: Based on the review of the report and the comments from the secondary review (comments from consult in attachment) of this study by Dr. Ameeta Parekh, Clinical Pharmacologic Team Leader in the Division of Urologic and Reproductive Drug Products (DURDP), the following wording is recommended:

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

Sponsor's Proposal (Page 18, 5th paragraph)



Sponsor's Proposal (Page 33; 4th paragraph)

CellCept Capsules, Tablets and Oral Suspension: The initial oral dose of CellCept should be given as soon as possible following renal or cardiac transplantation.

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Reviewer's Comments: The supporting information for the deletion proposed was originally submitted to NDA 50,722 and reviewed by Dr. Chandra Sahajwalla. Based on a look at his review, it is evident AUC may be a better predictor of efficacy (biopsy proven rejection), however, whether C_{max} is important or not, especially during the early transplant period has not been conclusively shown. Therefore, the following wording is recommended

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

Sponsor's Proposal (Page 33, 5th paragraph)

Patients With Hepatic Impairment:

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**APPEARS THIS WAY
ON ORIGINAL**

/S/

2/19/2000

Kofi A. Kumi, Ph.D.
Reviewer
HFD-590 Section
Division of Pharmaceutical Evaluation III
OCPB

Concurrence:

/S/ 7/19/00

Funmi Ajayi, Ph.D.
Team Leader
HFD-590 Section
Division of Pharmaceutical Evaluation III
OCPB

CC: NDA 50,740 SLR-004
HFD-590

HFD-880

CDR

/MO/J Korivick
/PM/M Bacho
/TLDPEIII/F Ajayi
/DPEIII/K Kumi
/Division Files
/B Murphy

ATTACHMENT

DURDP Consult

The results showed no clinically significant change (discussion with Dan Davis) that would indicate OC failure. Plasma concentration profiles for the OCs were similar with and without MMF. The following comments should be taken into consideration for general conclusions and labeling:

COMMENTS/SPECIAL INSTRUCTIONS:

Although no clinically relevant changes were observed in the LH, FSH and progesterone upon coadministration of the studied OCs with MMF, this data is derived from a limited number of subjects on each OC. Dan Davis and I have discussed the proposed wording in the label by Dr. Kofi Kumi and agree that the label should specify the OCs studied. A further minor clarification may be considered within Dr. Kumi's recommendation as follows: "...CellCept may not have any influence on the ovulation suppressing action of the — oral contraceptives; however...".

SIGNATURE OF REVIEWER: Ameeta Parekh

SIGNATURE OF TEAM LEADER: ~~_____~~

Date 7/5/00

Date 7/6/00

CC: HFD 580(Rumble, Davis) HFD 870 (Huang, Hunt, Parekh),
HFD 880 (Kumi, Ajayi)

**APPEARS THIS WAY
ON ORIGINAL**

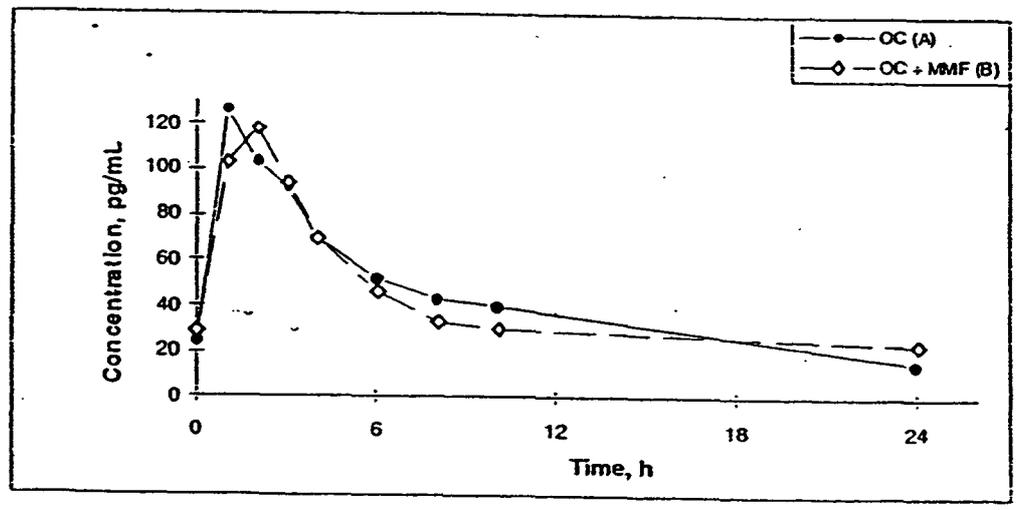
3 ket also used for

List of Active Ingredients in Oral Contraceptive Formulations Used By Patients

Trade Name	Used by Patients (No.)	ethinylestradiol (µg)	levonorgestrel (µg)	desogestrel (µg)	gestodene (µg)
Cycleane 20	104, 203	20		150	
Cycleane 30	103	30		150	
Harmonet	205	20			75
Marvelon	401, 402, 403	30		150	
Mercilon	106, 107, 108, 201	20		150	
Mimidril	101, 102, 109, 206, 208	30	150		
Triminulet ¹	202	30, 40, 30			50, 70, 100
Trinordiol ¹	204	30, 40, 30	50, 75, 125		
Varoline	105	30		150	

¹ Triphasic oral contraceptives

Mean Concentration Versus Time Profiles for Ethinylestradiol During Segments 1 and 2 (n=15)



~~Figure 4~~ Mean Concentration Versus Time Profiles for Levonorgestrel During Segments One and Two (n=5)

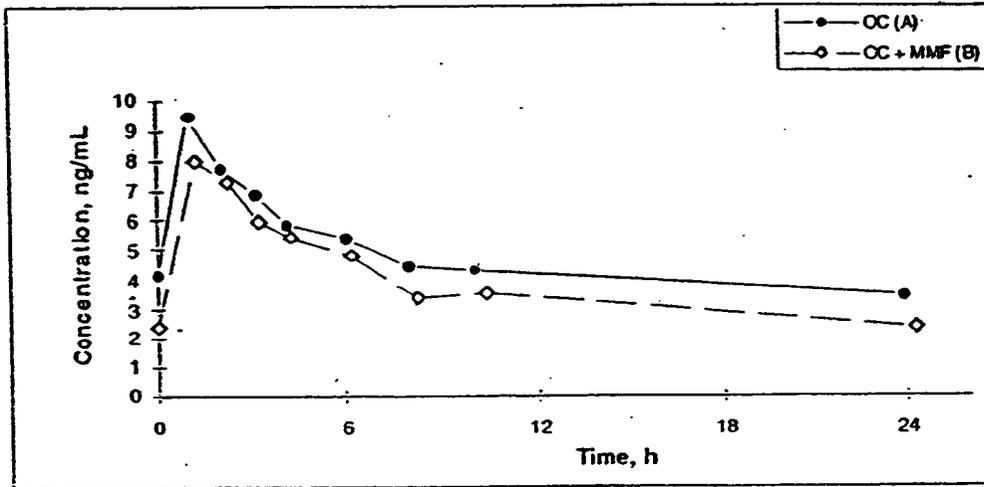
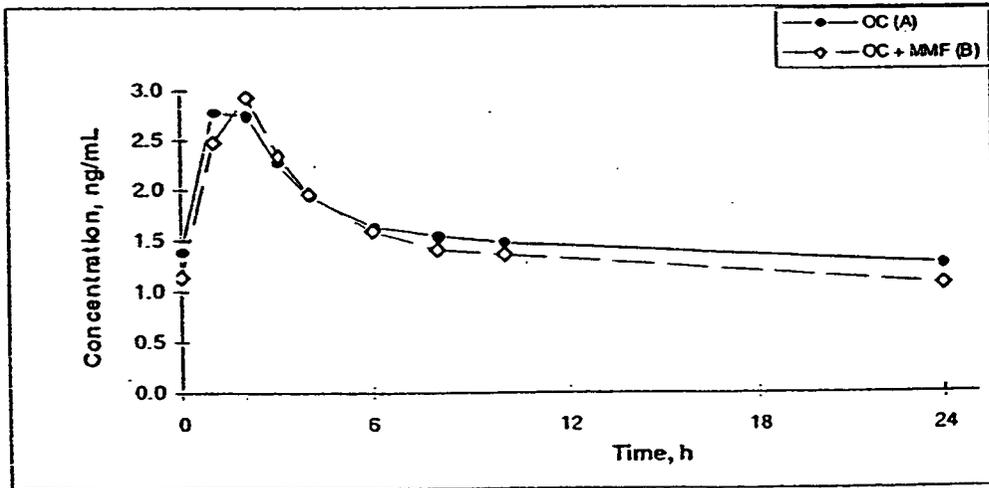


Figure 5 Mean Concentration Versus Time Profiles for 3-Keto-Desogestrel During Segments One and Two (n=10)



Descriptive Statistics of the Pharmacokinetic Parameters for Ethinylestradiol By Segment

Parameter	Ethinylestradiol n = 15	
	Segment 1 Oral Contraceptive Alone	Segment 2 Oral Contraceptive plus MMF
AUC(0-24h)		
Mean (pg h/mL)	952	984
Min - Max (pg h/mL)	288 - 1781	226 - 2196
SD (pg h/mL)	524	614
%CV	55.0	62.4
C_{max}		
Mean (pg h/mL)	131	134
Min - Max (pg h/mL)	56.1 - 235	55.2 - 247
SD (pg h/mL)	50.8	51.8
%CV	38.9	38.6
T_{max}		
Median (h)	1.03	1.97
Min - Max (h)	0.917 - 2.98	0.933 - 3.17

Table 9 Descriptive Statistics of the Pharmacokinetic Parameters for Levonorgestrel and 3-Keto-Desogestrel in Segments One and Two

Parameter	Levonorgestrel n = 5		3-Keto-desogestrel n = 10	
	Segment 1 Oral Contraceptive Alone	Segment 2 Oral Contraceptive plus MMF	Segment 1 Oral Contraceptive Alone	Segment 2 Oral Contraceptive plus MMF
AUC(0-24h)				
Mean (ng·h/mL)	113	90.4	38.4	35.4
Min - Max (ng·h/mL)	62.3 - 190	66.7 - 117	20.9 - 56.3	24.2 - 65.4
SD (ng·h/mL)	52.9	22.4	11.9	12.4
%CV	46.9	24.8	31.0	35.0
C_{max}				
Mean (ng·h/mL)	9.49	9.09	3.14	3.19
Min - Max (ng·h/mL)	5.28 - 15.4	7.12 - 12.5	2.13 - 4.02	2.15 - 4.50
SD (ng·h/mL)	4.16	2.02	0.546	0.804
%CV	43.8	22.2	17.4	25.2
T_{max}				
Median (h)	0.983	0.967	1.48	1.98
Min - Max (h)	0.917 - 1.10	0.917 - 3.17	0.967 - 3.00	0.917 - 3.00

Table 10 Ratios of AUC_(0-24h) and C_{max} for Ethinylestradiol, Levonorgestrel, and 3-Keto-Desogestrel During Segment 2 (Combined Treatment) Relative to Segment 1 (Oral Contraceptives Alone)

Ethinylestradiol:	Log Transformed Scale			
	Ratio X 100 (%)	95% CL	90% CL	Intra-individual CV (%)
AUC _(0-24h)	100.0	85.3 - 117.2	87.7 - 114.0	20
C _{max}	102.5	89.0 - 118.1	91.3 - 115.2	18
Levonorgestrel:				
AUC _(0-24h)	85.1	51.7 - 139.0	58.1 - 124.6	28
C _{max}	101.7	64.8 - 159.4	72.0 - 143.6	26
3-Keto-Desogestrel:				
AUC _(0-24h)	92.5	74.9 - 114.1	78.0 - 109.7	21
C _{max}	100.1	81.6 - 122.7	84.8 - 118.0	20