Table 77 reveals the cumulative hematology adverse event data from the primary and extension study of 058. The drops in hemoglobin and hematocrit are worth noting, specially given the degree of change from baseline in order to trigger inclusion in the definition of adverse event (≥6 % for hematocrit and ≥2 gm/dL for hemoglobin). These changes however, may not relate to GI blood loss. They may represent hemodilution in view of the edema related adverse events discussed in the primary reviewer's report.

Table 77 (% with specific adverse event)

	Primary 6-week data				Extension data		
	Placebo N=52	Vioxx 12.5 N=118	Vioxx 25 N=56	Nabumetone N=115	Vioxx 12.5 N=95	Vioxx 25 N=50	Nabumetone 92
Hemoglobin Drop of ≥2 gm/dl	0	0.8	5.6	0	1.1	10.2	0.8
Hematocrit Drop of ≥ 6%	o	0.8	5.6	0	2.1	8.2	1.6

The increase over time in the adverse event profile related to hemoglobin and hematocrit in the elderly population may have clinical relevance in post marketing experience.

Recommendations for Regulatory Action:

1. It is recommended that the sponsor be permitted to claim that fewer gastroduodenal ulcers are associated with the use of Vioxx 25 or 50 mg daily compared to ibuprofen 2400mg in three divided doses daily when used from 6 to 24 weeks duration. This recommendation is based on studies 044 and 045.

2. It is recommended that the sponsor be permitted to claim that occult GI blood loss over a 4-week interval is similar in patients treated with Vioxx 25 and 50mg daily compared to placebo and significantly less than ibuprofen. This recommendation is based on results from study 050.

3. It is recommended that the sponsor not be permitted to make claims regarding superiority in the rates of "PUBs", or GI adverse events compared to NSAIDs because the data submitted in support of these claims are not adequate.

4. It is recommended that the sponsor not be permitted to make claims regarding comparability to placebo for several reasons.
   a) There was a consistent dose related rise in ulcer rates associated with the use of Vioxx 50 mg compared to 25 mg at all intervals tested.
   b) Placebo comparability was evaluated statistically at one of 2 time intervals and one of 2 proposed dosages.
   c) No placebo comparisons beyond 12 weeks were available for this drug dose proposed for treatment of a chronic condition.
   d) Populations differed significantly between the two studies, 044 and 045, as did the placebo ulcer rates. Trends in the placebo associated ulcer rate compared to the Vioxx associated ulcer rates were in opposite directions in the two studies. Thus, the studies were not replicative.

/S/

Lawrence Goldkind M.D.

Concur. May 13, 1999

/S/

cc:
NDA 21-042
NDA 21-042
HFD-180
HFD-180/LTalarico /S/ 5-13-99
HFD 180/HGallo-Torres
HFD180/Lgoldkind
HFD-180/CSO Consult File
F/t jgw 5/13/99
C/21042905.OLK

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S CONSULT REVIEW

NDA:	21-042 21-052
Sponsor:	Merck & Co. Inc.
Drug:	Vioxx™ (Rofecoxib, MK-0966)
Proposed Clinical Indication:	1) Treatment of Osteoarthritis 12.5 to 25 mg per day 2) Relief of Acute Pain and Treatment of Primary Dysmenorrhea 50 mg daily, then 25 to 50 mg daily for 5 days
Proposed Indication:	Effect of Vioxx™ on Platelet Function
Submission Date:	11/23/98
Date Assigned:	1/25/99
Date Completed:	4/6/99
Reviewer:	Ann Farrell, M.D.

Background

Vioxx™ is a cyclooxygenase-2 (COX-2) specific inhibitor (C-2SI) being developed by Merck & Co. for the treatment of osteoarthritis, acute pain, and primary dysmenorrhea.

The purpose of this consult review is to assess the effect of Vioxx™ on platelet function. Additionally a review of the computerized database was performed to assess the effect of Vioxx™ on other hematologic parameters.

The most commonly used medications for the treatment of osteoarthritis, acute pain, and primary dysmenorrhea are non-steroidal anti-inflammatory agents (NSAIDS) and aspirin. These compounds suppress inflammation through non-specific inhibition of the cyclooxygenase enzyme. Cyclooxygenase is responsible for the generation of prostaglandins. Aspirin results in irreversible inhibition of cyclooxygenase while the nonsteriodal anti-inflammatory agents result in reversible inhibition.

Prostaglandins mediate cell function. Stimuli cause the release of arachidonic acid from cell membrane phospholipids by Phospholipase A_2 and other enzymes. Subsequently arachidonic acid is converted to prostaglandin precursor (PGH_2) by the cyclooxygenase (COX) enzyme. Two isoforms of the COX enzyme have been identified.

Cyclooxygenase-1 (COX-1) is constitutively expressed and enzymatically active in most tissues throughout the body. This isoform regulates the production of prostaglandins important for the maintenance of homeostatic function of specific organs and tissues. The COX-2 isoform can be upregulated during inflammation and other conditions. Inhibition of prostaglandin production can result in both beneficial as well as adverse effects.

Non-selective COX inhibitors are associated with beneficial effects such as the prevention of upregulation of COX-2 thereby reducing the inflammation. Nonselective COX inhibitors are associated with adverse effects such as inhibition of platelet thromboxane A_2 (TXA_2) production

resulting in impairment of platelet aggregation and hemostasis arising from inhibition of COX-1. Nuclear structure permits the upregulation of COX-2, an inducible enzyme. Platelets lack a nucleus and possess only COX-1 activity. Lacking a nuclear structure they are unable to upregulate COX-2. Specific COX-2 inhibitors may offer a selective advantage in preventing the upregulation of the COX-2 without affecting the function of the COX-1. This advantage may prevent the severe GI toxicity/hemorrhagic complications associated with non-selective COX inhibitors.

The sponsor evaluated the effect of Vioxx™ on platelet function through prostaglandin production assays, platelet aggregometry, and the bleeding time.

Assessment of COX-1 activity

COX-1 activity can be assessed by determining prostaglandin metabolites in serum and urine. Thromboxane A_2 (TXA_2) production in platelets is a function of COX-1 activity. TXA_2 is relatively unstable and undergoes hydrolysis to thromboxane B_2 (TXB_2), an inactive metabolite. TXB_2 may be measured in serum *ex vivo* and its production can be used as a marker for COX-1 activity in platelets. Actual TXA_2 synthesis *in vivo* is reflected by assays for the major urinary TX metabolite, 11-dehydrothromboxane B_2. A selective COX-2 inhibitor should not affect the serum and urinary levels of the thromboxanes.

Assessment of COX-2 activity

Lipopolysaccharide (LPS)-induced Prostaglandin E_2 (PGE_2) is a prostaglandin produced by the COX-2 isoform. Monocytes and macrophages express COX-2 when induced by LPS *in vitro*. Serum levels may provide an assessment of COX-2 activity *ex vivo*. Urinary 2,3-Dinor-6-Keto Prostaglandin $F_{1\alpha}$ and 6-Keto Prostaglandin $F_{1\alpha}$ levels are an index of systemic biosynthesis and metabolism. A selective COX-2 inhibitor should result in significant inhibition of serum PGE_2 and urinary $PGF_{1\alpha}$ production.

Four studies assessed the effects of MK-0966 on platelet function. The studies are listed in the following table and the results of each study are summarized.

Protocol number	Population	Treatment Groups and Regimens	Treatment Period	Outcome Measures
P002 (n=8)	Healthy males	Fasted state -MK-0966 5mg -MK-0966 2 x 5 mg -MK-0966 25 mg -MK-0966 2 x 25 mg -MK-0966 125 mg -MK-0966 2 x 125 mg -MK-0966 250 mg -MK-0966 2 x 250 mg -MK-0966 4 x 250 mg -Placebo Fed State -MK-0966 250 mg -Placebo	Each treatment lasted 1 day with a wash-out period of at least six days for treatments for the fasted state and a wash-out period of at least nine days for the fed state	Serum TXB_2 and LPS-induced whole blood PGE_2, laboratory data
P005 (n=31)	Healthy males	-MK-0966 25 mg -MK-0966 100 mg -MK-0966 250 mg -MK-0966 375 mg -Placebo	Once daily dose Day 1 and Days 3 to 14	Serum LPS-induced PGE_2 and TXB_2 levels, laboratory data
P061 (n=76)	Healthy females	-MK-0966 12.5 mg -MK-0966 25 mg -Diclofenac 50 mg -Ibuprofen 800 mg -Naproxen sodium 550 mg -Meloxicam 15 mg -Placebo	Daily medication given for 5 days plus morning dose on Day 6	Serum LPS-induced PGE_2 and TXB_2 levels, bleeding time, urinary prostanoids, laboratory data

P063 (n=24)	Healthy males and females	-MK-0966 50 mg + Aspirin 81 mg -Placebo + Aspirin 81 mg 12 per group	Either Placebo or MK-0966 daily for 10 days with Aspirin 81 mg daily Day 4-10	Serum TXB_2, platelet aggregation, serum hgb, platelet count, wbc (total and differential), urinalysis

Study Protocol P002

Pertinent Objectives: To evaluate the safety and tolerability of rising single oral doses of MK-0966, and to assess the effect of MK-0966 on serum TXB_2, LPS-induced whole blood PGE_2, and bleeding time

Study Design: Double-blind, randomized, placebo-controlled, rising single oral dose study to assess the safety, tolerability, pharmacokinetics, and biochemical activity of MK-0966.

Subjects: 16 healthy male volunteers aged 20 to 25 without a history of gastrointestinal abnormality, surgery, or bleeding, and willing to avoid excess alcohol or strenuous physical activity

Study Drug: Placebo, MK-0966 5 mg to 1000 mg daily in fasted state, MK-0966 250 mg daily in fed state

Study Plan: Serum TXB_2 and LPS-induced PGE_2 were measured for each subject predose, at 1.5, 4 and 8 hours postdose following administration of varying doses of MK-0966 and placebo. Bleeding times were performed at the two highest dose levels.

Results:

Effect of MK-0966 on Serum TXB_2 inhibition: The results are summarized in tables 11 and 12.

Table 11

Summary Statistics for Percent Inhibition of Serum TXB_2 at Each Postdose Time Point

Panel: Treatment	N	Mean[2]	Approximate Between-Subject CV (%)[3]	Median[1]	Min[2]	Max[2]	Difference From Placebo[1] in Percent Inhibition: Mean[1]	90% CI[2]
1.5 Hours Postdose								
A: Placebo	8	6.5	24.5	5.7			.	.
A: 5 mg	6	1.5	10.8	2.6			-5.4	(-25.5, 11.5)
A: 25 mg	6	-6.2	24.2	-6.8			-13.5	(-35.2, 4.7)
A: 125 mg	6	13.0	22.1	7.1			7.0	(-10.8, 21.9)
A: 500 mg	6	15.3	13.5	16.9			9.5	(-7.8, 24.0)
B: Placebo	8	13.8	16.5	13.3			.	.
B: 10 mg	6	12.3	11.3	10.2			-1.7	(-21.1, 14.6)
B: 50 mg	6	20.4	13.8	18.2			7.6	(-10.0, 22.4)
B: 250 mg	6	11.8	23.0	4.8			-2.3	(-21.8, 14.1)
B: 1000 mg	6	7.7	10.8	7.1			-7.1	(-27.6, 10.1)
Pooled within-subject CV (%)[1] = 19.2								
4 Hours Postdose								
A: Placebo	8	-2.2	28.4	5.4			.	.
A: 5 mg	6	-0.5	12.5	8.3			1.7	(-20.7, 19.9)
A: 25 mg	6	4.2	31.6	1.1			6.2	(-15.1, 23.6)
A: 125 mg	6	10.5	17.3	5.6			12.4	(-7.5, 28.6)
A: 500 mg	6	-1.7	12.4	-4.0			0.5	(-22.2, 18.9)
B: Placebo	8	0.5	14.4	-0.2			.	.
B: 10 mg	6	4.7	34.7	5.6			4.3	(-17.5, 22.0)
B: 50 mg	6	14.4	15.7	11.7			14.0	(-5.6, 29.9)
B: 250 mg	6	8.1	42.4	-8.5			7.6	(-13.3, 24.7)
B: 1000 mg	6	13.7	11.2	14.4			13.3	(-6.4, 29.4)
Pooled within-subject CV[1] (%) = 22.5								

Table 11 (Cont.)

Summary Statistics for Percent Inhibition of Serum TXB_2 at Each Postdose Time Point

Panel: Treatment	N	Mean[2]	Approximate Between-Subject CV (%)[3]	Median[1]	Min[2]	Max[2]	Difference From Placebo[1] in Percent Inhibition: Mean[1]	90% CI[2]
8 Hours Postdose								
A: Placebo	8	-13.7	19.7	-10.6			.	.
A: 5 mg	6	-10.4	9.1	-8.9			2.9	(-10.2, 14.4)
A: 25 mg	6	-36.1	16.5	-41.0			-19.7	(-35.7, -5.5)
A: 125 mg	6	-8.0	23.2	-8.8			5.0	(-7.7, 16.3)
A: 500 mg	6	-13.2	9.4	-12.9			0.4	(-12.9, 12.2)
B: Placebo	8	-12.4	14.2	-9.2			.	.
B: 10 mg	6	-14.2	14.7	-14.8			-1.7	(-15.3, 10.4)
B: 50 mg	6	-0.3	10.9	2.3			10.7	(-1.3, 21.3)
B: 250 mg	6	-15.1	10.0	-14.4			-2.4	(-16.1, 9.7)
B: 1000 mg	6	-14.6	13.7	-16.5			-2.0	(-15.7, 10.1)
Pooled within-subject CV[1] (%) = 13.9								

[1] Difference in percent inhibition of TXB_2 in all subjects receiving placebo within a panel.
[2] Back transformed from log-percentage summaries.
[3] Between-subject SD in the log-percentage scale X 100.
[4] RMSE in the log-percentage scale X 100.

Data Source: [2.2]

Sponsor's table

No significant inhibition of TXB_2 was observed in the pooled data from all patients except for the 25 mg group. The consistency of this result for other dosage groups and the lack of a dose response relationship for TXB_2 do not provide an explanation for the observed result with the 25 mg group. Table 11 with the pooled data from all patients demonstrates a lack of significant COX-1 inhibition.

Table 12

Summary Statistics for WAI and I_{max} of Serum TXB_2

Panel: Treatment	N	Mean[‡]	Approximate Between-Subject CV (%)[§]	Median[‡]	Min[‡]	Max[‡]	Difference From Placebo[*] in Percent Inhibition	
							Mean[‡]	90% CI[b]
WAI (%)								
A: Placebo	8	-4.5	22.9	-0.9			.	.
A: 5 mg	6	-3.3	9.2	-4.7			1.1	(-13.5, 13.8)
A: 25 mg	6	-11.0	21.2	-13.1			-6.2	(-21.9, 7.4)
A: 125 mg	6	4.3	11.7	4.7			8.4	(-5.1, 20.2)
A: 500 mg	6	-2.3	8.3	-2.9			2.2	(-12.3, 14.7)
B: Placebo	8	-1.5	9.5	-1.8			.	.
B: 10 mg	6	-0.6	20.8	0.5			0.9	(-13.7, 13.6)
B: 50 mg	6	10.6	8.6	8.7			11.9	(-1.1, 23.2)
B: 250 mg	6	0.2	22.3	-7.6			1.6	(-12.9, 14.3)
B: 1000 mg	6	3.7	9.8	3.9			5.1	(-8.9, 17.3)
Pooled within-subject CV (%)[¶] = 15.1								
I_{max} (%)								
A: Placebo	8	7.6	24.7	8.7			.	.
A: 5 mg	6	4.9	8.1	4.0			-3.0	(-25.9, 15.8)
A: 25 mg	6	10.2	30.6	1.1			2.8	(-18.8, 20.5)
A: 125 mg	6	23.6	19.1	26.7			17.3	(-1.1, 32.4)
A: 500 mg	6	15.3	13.5	16.9			8.4	(-12.0, 25.0)
B: Placebo	8	15.7	14.7	16.6			.	.
B: 10 mg	6	19.5	20.2	17.2			4.6	(-16.7, 22.0)
B: 50 mg	6	23.3	16.3	18.2			9.1	(-11.2, 25.6)
B: 250 mg	6	22.6	37.9	12.9			8.2	(-12.2, 24.9)
B: 1000 mg	6	15.3	9.6	14.9			-0.5	(-22.9, 17.8)
Pooled within-subject CV (%)[¶] = 22.1								

[*] Difference in percent inhibition of TXB_2 in all subjects receiving placebo within a panel.
[‡] Back transformed from log-percentage summaries.
[§] Between-subject SD in the log-percentage scale.
[¶] RMSE in the log-percentage scale.

Data Source: [2.2]

Sponsor's table

Effect of MK-0966 on LPS-induced PGE_2: The results are summarized in table 13.

Table 13

Summary Statistics for Percent Inhibition in LPS-Induced Whole Blood PGE_2 at 1.5, 4, and 8 Hours Postdose

Panel: Treatment	N	Mean[†]	Approximate Between-Subject CV (%)[§]	Median[‡]	Min[‡]	Max[‡]	Difference From Placebo[†] in Percent Inhibition: Mean[‡]	p-Values	90% CI[‡]
1.5 Hours Postdose									
A: Placebo	8	11.9	64.6	3.6					
A: 5 mg	6	69.8	47.5	67.7			65.7	0.003	(39.7, 80.5)
A: 25 mg	6	49.6	73.9	49.6			42.8	0.103	(-0.5, 67.5)
A: 125 mg	6	16.0	30.4	23.8			4.6	0.888	(-67.6, 45.7)
A: 500 mg	6	84.1	72.0	84.9			82.0	<0.001	(68.3, 89.7)
B: Placebo	8	-14.2	69.5	-25.8					
B: 10 mg	6	5.8	37.2	8.4			17.4	0.570	(-45.1, 53.0)
B: 50 mg	6	51.9	40.8	56.0			57.9	0.014	(26.0, 76.0)
B: 250 mg	6	95.8	90.1	95.6			96.3	<0.001	(93.5, 97.9)
B: 1000 mg	6	91.9	86.5	91.8			92.9	<0.001	(87.5, 96.0)
Pooled within-subject CV (%)[¶] = 62.0									
4 Hours Postdose									
A: Placebo	8	-7.1	55.6	-5.7					
A: 5 mg	6	35.6	17.9	36.8			39.9	0.058	(6.8, 61.2)
A: 25 mg	6	64.7	40.8	63.8			67.0	<0.001	(48.8, 78.7)
A: 125 mg	6	45.5	27.5	44.3			49.1	0.013	(21.1, 67.2)
A: 500 mg	6	88.3	38.0	89.9			89.0	<0.001	(83.0, 92.9)
B: Placebo	8	-21.9	15.4	-23.3					
B: 10 mg	6	25.7	35.6	25.6			39.1	0.064	(5.5, 60.7)
B: 50 mg	6	63.5	38.3	62.8			70.1	<0.001	(53.6, 80.7)
B: 250 mg	6	85.2	124.4	76.7			87.9	<0.001	(81.2, 92.2)
B: 1000 mg	6	92.6	56.6	91.3			94.0	<0.001	(90.6, 96.1)
Pooled within-subject CV (%)[¶] = 48.2									

Table 13 (Cont.)

Summary Statistics for Percent Inhibition in LPS-Induced Whole Blood PGE_2 at 1.5, 4, and 8 Hours Postdose

Panel: Treatment	N	Mean[‡]	Approximate Between-Subject CV (%)[§]	Median[‡]	Min[‡]	Max[‡]	Difference From Placebo[†] in Percent Inhibition: Mean[‡]	p-Values	90% CI[‡]
8 Hours Postdose									
A: Placebo	8	-7.4	45.9	-2.8					
A: 5 mg	6	37.7	31.2	37.1			42.0	0.023	(14.5, 60.7)
A: 25 mg	6	48.8	36.7	51.9			52.3	0.003	(29.7, 67.7)
A: 125 mg	6	64.8	62.6	69.7			67.2	<0.001	(51.6, 77.7)
A: 500 mg	6	90.6	59.7	89.8			91.2	<0.001	(87.1, 94.0)
B: Placebo	8	12.7	22.5	-18.2					
B: 10 mg	6	-24.5	39.5	-21.6			-10.5	0.667	(-62.9, 25.0)
B: 50 mg	6	57.8	27.9	59.7			62.5	<0.001	(44.7, 74.6)
B: 250 mg	6	87.8	57.8	86.8			89.1	<0.001	(84.0, 92.6)
B: 1000 mg	6	95.5	48.0	95.0			96.0	<0.001	(94.1, 97.3)
Pooled within-subject CV (%)[¶] = 42.7									

† Difference in percent inhibition of PGE_2 in all subjects receiving placebo within a panel.
‡ Back transformed from log percentage summaries.
§ Between-subject SD in the log-percentage scale X 100.
¶ RMSE in the log-percentage scale X 100.

Data Source: {2.2}

Sponsor's table

Significant inhibition of COX-2 activity is reflected in the marked suppression of serum PGE_2 levels particularly 4 and 8 hours post-dose. The percent inhibition for 125 mg dose at 1.5 hours postdose did not significantly differ from placebo. The inhibition of COX-2 activity does not appear complete with the 5mg and 10 mg doses. Higher doses of MK-0966 produced statistically significant inhibition of LPS-induced PGE_2 (or COX-2 activity) compared to placebo.

A comparison of pooled data from all patients for serum $TXB_2$and PGE_2 results demonstrate that MK-0966 consistently produced inhibition of COX-2 activity while not significantly affecting COX-1 activity.

Bleeding Time: The rsults of Predose and Postdose Bleeding times for MK-0966 500 mg and 1000 mg doses and placebo are summarized in table 17.

Table 17

Summary Statistics for Bleeding Times in Periods 7 and 8

		Predose		3 Hours Postdose		Change	
Treatment(Panel)	N	Mean	SD	Mean	SD	Mean	SD
Placebo (A+B)	4	4.61	1.82	4.26	1.14	-0.34	0.71
500 mg (A)	6	5.06	1.12	4.80	0.65	-0.26	1.26
1000 mg(B)	6	5.32	1.08	5.20	1.27	-0.12	0.65

Data Source: [4.10]
Sponsor's table

High doses of MK-0966 did not appear to affect the bleeding time. Review of individual patient data performed predose and 3 hours post-dose for periods 7 (500 mg) and period 8 (1000 mg) did not reveal any significant changes in the bleeding time.

Individual Patient Data: There was significant variability for individual patient's serum TXB_2 serum levels at various doses. Some patients had markedly decreased TXB_2 levels at the 1.5 hr and 4 hr time periods, compared to predose levels. Neither a strict dose response nor predictable decrease in serum TXB_2 level could account for the variability within patients and among patients. This data suggests that some COX-1 inhibition MK-0966 may occur for individual patients.

Clinical Adverse Events: No adverse hematological events were reported.

Changes in other Laboratory Parameters: Patients experienced a slight decrease in their hemoglobin result over the course of the study. White blood cell count, platelet count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils did not appear to be affected by administration of MK-0966.

Conclusion: In this study, Vioxx™ demonstrated significant COX-2 inhibition. The pooled data of serum TXB_2 suggests no significant inhibition of COX-1 activity. When individual patients' serum TXB_2 levels are compared predose to several hours post-dose, some patients do experience up to a 60% decrease in serum TXB_2 levels. This observed decrease could not be predicted by a dose response relationship. Vioxx™ did not appear to affect bleeding time.

Study Protocol P005

Pertinent Objectives: To evaluate safety and tolerability of 13 daily oral doses of MK-0966 administered over a 14 day period, and to obtain information on the effect of multiple doses of MK-0966 on LPS-induced PGE_2, TXB_2, and bleeding time.

Study Design: randomized, double-blind, placebo-controlled, staggered incremental dose, parallel study group

Subjects: 31 healthy males without history of GI disease, bleeding, asthma, nasal polyps, intolerance to non-steriodal anti-inflammatory drugs, or reduced creatinine clearance (≤ 80 mL/min).

Study Drug: MK-0966 25 mg, 100mg, 250 mg, and 375 mg, placebo

Study Plan: Volunteers were given a dose on day 1 and Days 3 to 14. Hematological sampling times are listed below.

Test Sampling times	Serum LPS-induced PGE_2	Serum TXB_2	Bleeding time
Predose (Day –1) hour 0, 1.5, 4 and 8 hours	Yes	Yes	Yes, but only once Day –1
Predose Day 7	Yes	Yes	No
Pre dose Day 14 and 4, 8, and 24 hours postdose			Yes, but at 4 hours postdose

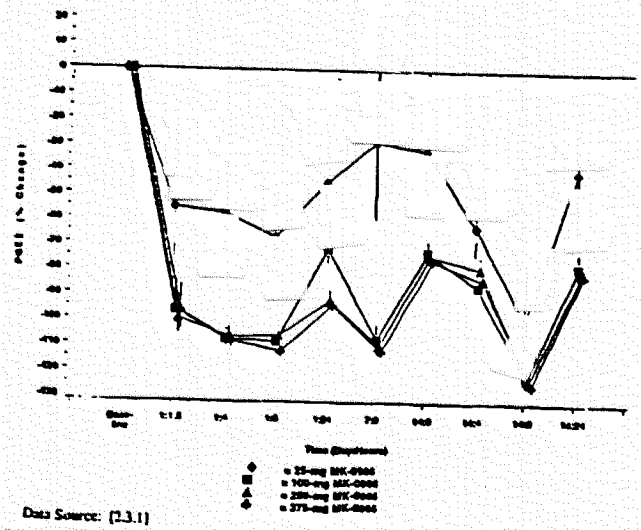
Reviewer's table

Results

The effect of MK-0966 on PGE_2 is summarized in Figure 7.

Figure 7

Effect of MK-0966 on Percent Change From Baseline PGE_2 on Days 1, 7, and 14 Expressed as Difference From Placebo (Mean ± 90% CI)



Data Source: [2.3.1]

Sponsor's graph