



Juan Carlos Pelayo, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel: (301) 594-5378; FAX: (301) 594-5494

Memorandum

FROM: Juan Carlos Pelayo, M.D., Medical Officer, HFD-110 *Juan Carlos Pelayo*

THROUGH: Charles Ganley, M.D., Medical Officer Group Leader, HFD-110 *Charles Ganley*

Raymond J. Lipicky, M.D., Director, Division of Cardio-Renal Drug Products *Raymond J. Lipicky*

TO: Sandra Cook, Health Project Manager, HFD-550

Maria L. Villalba, M.D., Medical Officer, HFD-550

John Hyde, M.D., Ph.D., Acting Deputy Division Director, HFD-550

Robert DeLap, M.D., Director, ODE V, and Acting Division Director Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

SUBJECT: Consultation NDA 21-042.

Review of Cardiovascular¹ and Renal Safety database.

NAME OF DRUG/SPONSOR: VIOXX™ (Rofecoxib) Tablets, MERCK Research Laboratories.

DATE NDA RECEIVED: December 23, 1998

DATE NDA ASSIGNED: December 28, 1998

DATE REVIEW STARTED: January 25, 1999

DATE REVIEW COMPLETED: April 30, 1999

CC:

Orig. to NDA 21-042

HFD-550

HFD-110

HFD-110 / J.C. Pelayo / C. Ganley

¹ The assessment of the cardiovascular safety of MK-0966 was limited to hypertensive- and edema-related adverse events.

Table Of Contents	Page(s)
1.0 Integrated Review Of Cardiovascular And Renal Safety	3,4
2.0 Summary Of Key Cardiovascular And Renal Adverse Findings	4-7
3.0 Background	7
4.0 Materials Utilized In Safety Review	8
5.0 Methodology For Safety Review	8
6.0 Indication	8
7.0 Proposed Labeling	9
8.0 Animal Pharmacology/Toxicology	9
9.0 Clinical Data Sources	
9.1 Primary Source Data	9,10
9.2 Special Studies Data	10
10.0 Demographics	10
11.0 Extent Of Exposure (Dose/Duration)	10,11
12.0 Labeling Review	11,12
13.0 Human Pharmacokinetic Considerations	12
14.0 Overdosage	12
15.0 Individual Clinical Pharmacodynamic/Pharmacokinetic Studies Report	
15.1 Pharmacodynamic Studies:	
15.1.1 Protocol #013	13-16
15.1.2 Protocol #065	16-20
15.1.3 Protocol #023	20-25
15.2 Pharmacodynamic Interaction Studies	
15.2.1 Protocol #054	25-27
15.3 Pharmacokinetic Studies	
15.3.1 Protocol #064	28-31
16.0 Individual Clinical Osteoarthritis Studies Report	
16.1 Six-Weeks Studies	
16.1.1 Protocol #010	32-35
16.1.2 Protocol #029	35-41
16.1.3 Protocol #033	41-49
16.1.4 Protocol #040	49-54
16.1.5 Protocol #058	54-58
16.2 Six-Months Studies	
16.2.1 Protocol #034	59-69
16.2.2 Protocol #035	69-79
16.2.3 Protocol #044	79-91
16.2.4 Protocol #045	91-104
16.3 Six-Months to 86-Weeks Studies	
16.3.1 Protocol #029C	105-111
16.3.2 Protocol #034C	111-119

1.0 Integrated Review Of Cardiovascular And Renal Safety

Pharmacodynamic Studies: The sponsor conducted three pharmacodynamic studies, which were aimed to investigate the effect of MK-0966 on renal function. The effect of a single doses of 250 mg MK-0966, 75 mg indomethacin, and placebo on renal function in healthy adult men and women, age 62 to 79 years old, on a low sodium diet (30 mEq/day) was assessed in Study protocol #013. MK-0966 effected qualitatively and quantitatively similar changes (i.e., reductions), to indomethacin, on glomerular filtration rate (GFR) and urinary sodium excretion, and this effect on both variables was statistically significantly different from placebo. There were not cardiovascular and/or renal safety concerns revealed in this study.

Study protocol #065 compared the effects of multiple doses of placebo, 50 mg indomethacin 3 times a day, 12.5 mg MK-0966 once a day, and 25 mg MK-0966 once a day on renal function in 60 generally healthy adult men and women 65 to 80 years of age on a restricted sodium intake (30 mEq sodium/day). In comparison to placebo only MK-0966 (12.5 mg and 25 mg a day) effected a statistically significant reduction in GFR (assessed by the clearance of iothalamate). The reductions in urinary sodium excretion associated with MK-0966 treatment, both 12.5 mg and 25 mg, albeit they did not reach statistical significant they were numerically larger than placebo or indomethacin. Furthermore, MK-0966 25 mg/day and indomethacin 50 mg three times a day were associated with increases in serum potassium, which were significantly different from placebo and MK-0966 12.5 mg/day. No cardiovascular and/or renal safety concerns were raised in this study.

Study protocol #023 was a 2-week, double-blind, parallel-group study of renal function which demonstrated that MK-0966 50 mg daily was associated with a sodium-retaining effect in healthy elderly subjects maintained on a high-salt diet (200 mEq sodium/day). This effect of MK-0966 was not significantly different from that of indomethacin. Only indomethacin administration reduced the creatinine and iothalamate clearances, and the excretion of urinary 11-dehydro thromboxane B2. However, MK-0966 and indomethacin were associated with significant reductions at Day 13 in the excretion of urinary 6-keto-PGF_{1α} and PGI-M. No renal- and/or cardiovascular related adverse experiences in clinical or laboratory safety tests were observed.

Collectively, the results from the pharmacodynamic studies indicate that MK-0966, a COX-2 inhibitor, influences renal function in a way resembling indomethacin, a dual COX-1/COX-2 inhibitor, in that its administration was associated with reductions in GFR, urinary sodium excretion, and urinary prostaglandins excretion.

Pharmacodynamic Interaction Studies: Non-steroidal anti-inflammatory drugs (NSAIDs), are known to attenuate the antihypertensive effects of ACE inhibitors, β-blockers and diuretics. Study protocol #054 was designed to determine the influence of MK-0966 on blood pressure in patients with mild-to-moderate hypertension treated with the commonly used ACE inhibitor, benazepril. Similarly to indomethacin, MK-0966 attenuated the antihypertensive effect of the ACE inhibitor benazepril. MK-0966 and indomethacin were associated with mean (90% CI) increases (relative to placebo) in 24-hour mean SBP of 4.5 (2.2, 6.8) and 2.0 (-0.3, 4.4) mm Hg, respectively, and increases in the 24-hour mean MAP of 2.8 (1.0, 4.6) and 1.4 (-0.4, 3.2) mm Hg, respectively. Of note, two events of increased serum creatinine, and one event of increased potassium were reported.

This pharmacodynamic interaction study revealed the capacity of MK-0966, shared by other NSAIDs, to attenuate the antihypertensive effect of the ACE inhibitor benazepril in patients with mild-to-moderate hypertension.

Pharmacokinetic Studies: Study protocol #064 was designed to determine the effect of renal insufficiency and hemodialysis on the plasma pharmacokinetics of MK-0966 after a single oral dose of 50 mg. Comparisons of plasma pharmacokinetic parameters, i.e., AUC_(0-48 hr), AUC_(0-∞ hr), C_{max}, T_{max}, t_{1/2}, and *in vitro* protein binding between patients with end-stage renal disease on hemodialysis and healthy volunteers, indicated that renal insufficiency has no marked effect on the pharmacokinetics of oral MK-0966. The dialysis clearance of MK-0966 was approximately 40 ml/min regardless of when the dialysis was initiated (48 or 4 hours postdose).

Osteoarthritis Studies: The integrated review of the cardiovascular and renal safety of MK-0966 derived from this clinical database is provided in the section **Summary Of Key Cardiovascular And Renal Adverse Findings**.

2.0 Summary Of Key Cardiovascular And Renal Adverse Findings

Two related but unique isozymes of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), catalyze human prostaglandin synthesis. Recent studies, using RT-PCR, *in situ* hybridization and immunohistochemistry, have demonstrated that both isozymes are present in the kidneys of humans albeit with differences in their localization and level of basal expression². The distinct renal localization of these isozymes provides the basis for potential differences in the renal effects of drugs possessing specific inhibitory actions on cyclooxygenases. MK-0966 is a COX-2 inhibitor, and nonselective COX-1/COX-2 inhibitors, i.e., non-steroidal anti-inflammatory drugs (NSAIDs), are known to produce cardiovascular and renal effects. It is well established that these therapeutic agents have the potential for causing hypertension, fluid retention (i.e., edema), hyperkalemia, serum creatinine increased, proteinuria, nephrotic syndrome (i.e., minimal change disease, membranous nephropathy), interstitial nephritis, renal papillary necrosis, and acute/chronic renal failure.

Therefore the results of the clinical trials in humans using MK-0966 should help to determine whether this highly selective COX-2 inhibitor have effects on renal function which differ from the currently available NSAIDs with dual COX-1/COX-2 inhibitory capacity.

Key cardiovascular³ and renal adverse findings were identified from the clinical database based on consistency across studies and evidence of occurrence in a dose-dependent manner in most studies.

Analysis of the clinical database indicates that there is an unequivocal association between MK-0966 administration and the occurrence of cardiovascular and renal adverse events in a finite number of exposed individuals. Within the constraints of the available clinical database on MK-0966, it can be deduced that the salient cardiovascular and renal adverse events of MK-0966 are **hypertension, edema, serum creatinine increased, hyperkalemia, and proteinuria**. Of note, there were patients receiving MK-0966 that were discontinued from the clinical trials by the principal investigators because of hypertensive- or edema-related adverse experiences. In the current clinical trials, neither MK-0966 nor the active comparators were associated with cases of acute renal failure requiring dialysis support, interstitial nephritis, and nephrotic syndrome or renal papillary necrosis.

In the aggregate, the data allow to reach the conclusion that qualitatively the cardiovascular and renal "toxicity" of MK-0966, a purported COX-2 inhibitor, is readily distinguishable from placebo, but closely mimics that of other, already approved, nonselective COX-1/COX-2 inhibitors. Of note, the Medical Reviewer did not encounter, in the review of the clinical database, identifiable cardiovascular or renal adverse events specific to MK-0966.

Quantitatively there is evidence, in most studies, for the aforementioned key cardiovascular and renal adverse findings to occur in a dose-dependent manner with the administration of MK-0966⁴. Of note, in most of the studies⁵ the identified cardiovascular and renal toxicities associated with MK-0966, when administered at a dosage ranging from 25 to 50 mg/daily, occur at a higher rate than with the other tested comparators, i.e., ibuprofen, diclofenac, or nabumetone.

² Khan K.N.M., et al.: Toxicologic Pathology, Vol. 26, no. 5, pp. 612-620, 1998.

³ The assessment of the cardiovascular safety of MK-0966 was limited to hypertensive- and edema-related adverse events.

⁴ Albeit, it is not discussed in this review the rate of occurrence of the critical events is modified, upwards, by the time of exposure to MK-0966.

⁵ This statement applies to studies with drug exposure of greater than 6-weeks.

Unanswerable from the available clinical database however, is the question whether the noticed differences, between MK-0966 and the active comparators, in the rate of occurrence of the aforementioned adverse events, which themselves are surrogates for clinical morbidity⁶, would be translated overtime in clinically significant differences in cardiovascular and renal morbidity.

The aforementioned conclusions are illustrated in the following tables.

Table Study #058⁷, summarizes the incidence rates of key cardiovascular and renal adverse findings in elderly patients with osteoarthritis for the six weeks treatment period of Protocol #058. Treatment with MK-0966 at 25 mg was associated with incident rates for the aforementioned adverse events⁸ that were higher than placebo. Hypertension, edema, serum creatinine increased and hyperkalemia adverse events occurred in a dose-dependent manner with MK-0966.

Table Study #058. Number (%) Of Patients With Hypertensive- Or Edema-Type Adverse Experiences Or Laboratory Adverse Experiences (Intention-To-Treat Approach) 6-Week Base Study

Treatment	ΣHypertension n‡/N§ (%)	ΣEdema n‡/N§ (%)	Serum creatinine Increased n‡/N§ (%)	Hyperkalemia n‡/N§ (%)	Proteinuria n‡/N§ (%)
Placebo	1/52 (1.9)	3/52 (5.8)	0/52 (0.0)	0/52 (0.0)	1/52 (1.9)
MK-0966 12.5 mg	3/118 (2.5)	9/118 (7.6)	5/118 (4.2)	0/118 (0.0)	2/118 (1.7)
MK-0966 25 mg	2/54 (3.6)	6/54 (10.7)	3/54 (5.6)	2/54 (3.7)	0/54 (0.0)
Nabumetone 1500 mg	4/114 (3.5)	7/114 (6.1)	4/114 (3.5)	0/114 (0.0)	1/114 (0.9)

[Adapted from NDA 21-042. ‡Number of patients with adverse event. §Total number of patients. ΣHypertension = patients had adverse experiences under the broader term "blood pressure increased". ΣEdema = Peripheral edema+Edema+Fluid retention+Lower extremity edema+Hand swelling.]

In Table Study #044/045⁹, the results for the key cardiovascular and renal adverse findings for the 18-week treatment period of studies 044 and 045 are summarized. There was a dose-relationship for the rate of occurrence for the aforementioned adverse events¹⁰ with MK-0966. The incident rate for the key cardiovascular and renal adverse findings in the MK-0966 groups was higher than for placebo. At 50 mg MK-0966 caused hypertension, edema, serum creatinine increased and to a lesser extent hyperkalemia with a frequency higher than the active comparator ibuprofen.

⁶ With the exception of clinical edema.

⁷ The study had the following design: multicenter, double blind, placebo and active comparator controlled, parallel group, and randomized healthy men or women ≥80 years old, with a clinical and radiologic diagnosis of OA of the knee (tibio-femoral joint) or hip.

⁸ Except for proteinuria.

⁹ The studies had a double-blind (with in-house blinding), multicenter, parallel-group design; to investigate the effect of MK-0966 25 mg once daily, MK-0966 50 mg once daily, ibuprofen 800 mg 3 times daily (2400 mg), or placebo on the incidence of gastroduodenal ulcer following 12-24 weeks of treatment in patients with osteoarthritis.

¹⁰ Except for proteinuria.

Table Study #044/045. Number (%) Of Patients With Hypertensive- Or Edema-Type Adverse Experiences Or Laboratory Adverse Events Week 18 (Intention-to-Treat Approach)

Treatment	ΣHypertension n‡/N§ (%)	ΣEdema n‡/N§ (%)	Serum creatinine Increased n‡/N§ (%)	Hyperkalemia n‡/N§ (%)	Proteinuria n‡/N§ (%)
Placebo	13/358 (3.6)	10/361 (2.8)	1/363 (0.4)	9/363 (0.0)	2/363 (0.5)
MK-0966 25 mg	23/367 (6.4)	23/367 (6.3)	5/385 (1.3)	5/385 (0.8)	5/384 (1.3)
MK-0966 50 mg	31/358 (8.6)	30/349 (8.6)	11/372 (2.9)	4/371 (1.1)	3/371 (0.8)
Ibuprofen 2400 mg	17/360 (4.7)	16/361 (4.4)	6/377 (1.6)	3/371 (0.8)	4/371 (1.1)

[Adapted from NDA 21-042. ΣHypertension = Blood pressure increased, Borderline hypertension, Hypertension, Uncontrolled hypertension. ΣEdema = Edema, Fluid retention, Lower extremity edema, peripheral edema, Upper extremity edema. ‡Number of patients with adverse event. §Total number of patients.]

Table Study #034C¹¹ summarizes the key cardiovascular and renal adverse findings for the entire 12-month treatment period of the 1-Year Base Studies #s 034 and 035. In the MK-0966 groups, there was a dose-related incidence rate for all the cardiovascular and renal adverse events. And the rates of occurrence for these events at the 25 mg dosage of MK-0966 resemble those for the active comparator, diclofenac.

Table Study #034C. Number (%) Of Patients With Hypertensive- Or Edema-Type Or Laboratory Adverse Experiences Entire 1-Year Base Studies All Randomized Patients

Treatment	ΣHypertension n‡/N§ (%)	ΣEdema n‡/N§ (%)	Serum creatinine increased n‡/N§ (%)	Hyperkalemia n‡/N§ (%)	Proteinuria n‡/N§ (%)
MK-0966 12.5 mg	41/490 (8.4)	39/490 (8.0)	7/486 (1.4)	1/486 (0.2)	13/486 (2.7)
MK-0966 25 mg	46/489 (9.4)	45/489 (9.2)	12/483 (2.5)	5/483 (1.0)	19/484 (3.9)
Diclofenac 150 mg	32/498 (6.4)	29/498 (5.8)	13/496 (2.6)	3/496 (0.6)	17/495 (3.4)

[Adapted from NDA 21-042. ΣHypertension = Blood pressure increased+Borderline hypertension+Hypertension. ΣEdema = Edema+Hand swelling+Lower extremity edema+Peripheral edema. ‡Number of patients with adverse event. §Total number of patients.]

Because a recently approved COX-2 inhibitor, Celebrex™, was associated with hyperchloremia, serum bicarbonate and chloride results from the VIOXX™ clinical database were examined to determine whether that electrolyte derangement was unique to Celebrex™ or is a drug class effect. The sponsor obtained these measurements only in the six months studies protocol #s 044 and 045 (see Table below). To eliminate the potential confounding effect of differences in exposure¹², the data were examined up to 16 weeks of treatment.

The number (%) of patients exceeding predefined limits of change or extreme abnormal values for serum chloride and bicarbonate were similar among the groups. However, the paucity of information (i.e., short-term exposure of a few numbers of patients) on serum bicarbonate and chloride in the clinical database of VIOXX™ significantly hinders the assessment of the potential for this drug to significantly affect acid-base balance.

Reviewer's note: The fact that the current information on serum chloride and bicarbonate is deficient needs to be acknowledged in the package insert.

¹¹This study had a multicenter, double blind (with in-house blinding), active comparator (diclofenac sodium) controlled, and parallel group design. The subjects enrolled in the study were healthy men or women ≥40 years old, with clinical and radiographic diagnosis of OA of the knee or hip.

¹² As per protocol, no placebo values were recorded beyond 16 weeks.

Table Study #s 044 and 045. Number (%) Of Patients Exceeding Predefined¹³ Limits Of Change—Laboratory (Intention-To-Treat Approach) Week 16

Treatment	Serum Bicarbonate		Serum Chloride	
	Decrease ≥ 1.0 mEq/L and value $< LLN$	≤ 16 mEq/L	Increase ≥ 1.0 mEq/L and value $> ULN$	≥ 115 mEq/L
	n‡/N§ (%)	n‡/N§ (%)	n‡/N§ (%)	n‡/N§ (%)
Placebo	26/346 (7.5)	1/346 (0.3)	4/346 (1.1)	0/346 (0.0)
MK-0966 25 mg	24/376 (6.4)	5/376 (1.3)	11/376 (2.9)	2/376 (0.5)
MK-0966 50 mg	24/360 (6.7)	1/360 (0.3)	7/360 (1.9)	0/360 (0.0)
Ibuprofen 2400 mg	24/354 (6.8)	1/354 (0.3)	11/354 (3.1)	1/354 (0.3)

[FDA's analysis. ‡Number of patients meeting the predefined limit criteria. §Total number of patients with valid values of the laboratory or vital sign test. ULN = Upper limit of normal range. LLN = Lower limit of normal range.]

Reviewer's note: The sponsor did not measure serum magnesium and phosphorus during the clinical development of VIOXX™. However, these variables are currently being measured along with bone density in an ongoing study. The data from that study were not available for review. This lack of information prevents the assessment of the potential effects of VIOXX™ on their metabolism and to further characterize its safety profile. The importance of missing results on serum phosphorus in the clinical database of VIOXX™ is highlighted by the knowledge that the previously approved COX-2 inhibitor, Celebrex™, was associated with hypophosphatemia. A sentence regarding the lack of information on serum magnesium and phosphorus needs to be incorporated in the package insert.

In conclusion,

1. VIOXX™ caused vascular-renal adverse events, i.e., hypertension- and edema-type, serum creatinine increased, hyperkalemia, and to a lesser degree proteinuria in a dose-dependent manner.
2. The vascular-renal safety profile of VIOXX™ is clearly distinguishable from placebo, and is qualitatively similar to other NSAIDs.
3. The aforementioned adverse events occur at a higher rate with VIOXX™, at 50 mg, than with other NSAIDs at their recommended dosage. However, whether that will translate into clinically significant differences in vascular-renal morbidity cannot be determined from the current osteoarthritis clinical database.
4. Much larger clinical trials with longer exposure will be needed to detect whether VIOXX™ causes any of the severe renal syndromes seen, albeit less frequently, with other NSAIDs.

3.0 Background

Non-steroidal anti-inflammatory drugs (NSAIDs) are known therapeutic agents with the potential for causing significant cardiovascular and renal functional abnormalities/toxicity including hypertension, fluid retention (i.e., edema), hyperkalemia, serum creatinine increased, proteinuria, nephrotic syndrome (i.e., minimal change disease, membranous nephropathy), interstitial nephritis, papillary necrosis, and acute/chronic renal failure. Of note, the aforementioned adverse events have been described in patients, with or without obvious preceding renal disease.

The association of acute renal "insufficiency" defined as reduced glomerular filtration rate to acute renal failure with NSAIDs treatment is well established, and the prevailing notion is that of a functional/structural disorder which is, in part, hemodynamically mediated (i.e., vasomotor nephropathy). It has been postulated that the reduction in the synthesis of vasodilatory prostaglandins, elicited by the administration of NSAIDs, is central to the development of NSAIDs-induced acute renal "insufficiency." Patients at risk are mainly elderly and/or patients with medical conditions (i.e., renal insufficiency, nephrotic syndrome, glomerulonephritis, congestive heart failure, cirrhosis with

¹³ There was no pre-specified analysis of serum bicarbonate and chloride in the Data Analysis Plan for the phase II/III OA program, thus presented are the result of post hoc analyses.