MEDICAL OFFICER REVIEW
ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION—HFD-550

NDA #:	**21,042 (tablets), 21,052 (suspention)**
SUBMISSION DATE:	November 23, 1998
REVIEWER (For The Pain Indication):	Mordechai Averbuch, MD
PRODUCT:	**VIOXX (Rofecoxib)**
REVIEW DATE:	**March 15, 1999**
SPONSOR:	**Merck & Co.** P.O. Box 4 West Point, PA 19486 Phone (610) 394-2944
PHARMACOLOGICAL CATEGORY:	COX 2 Selective Inhibitor, Anti-inflammatory
PROPOSED INDICATIONS:	1) Acute or chronic use in the treatment of the signs and symptoms of osteoarthritis. 2) Relief of pain. 3) Treatment of primary dysmenorrhea.
DOSAGE FORM & ROUTE:	Oral tablets, 12.5 mg and 25 mg Oral suspension 12.5 mg/5ml and 25mg/5ml
CSO:	S. Cook

ATTENTION:

This review is for the section of this NDA submitted to support the indication of the management of pain and dysmenorrhea only. Studies supporting the indication of acute or chronic use in the treatment of the signs and symptoms of osteoarthritis, as well as other clinical studied conducted to support the safety profile of rofecoxib, are being reviewed by other medical reviewers.

RESUME:

Nine clinical trials have been conducted to support the management of pain and dysmenorrhea indications of which five are considered to be pivotal studies:

Five single dose, post third molar extraction studies, two of them are considered to be pivotal.
One multiple dose, 2 to5-day, post orthopedic surgery study that is considered to be pivotal.
Three dysmenorrhea studies of which two are considered to be pivotal.

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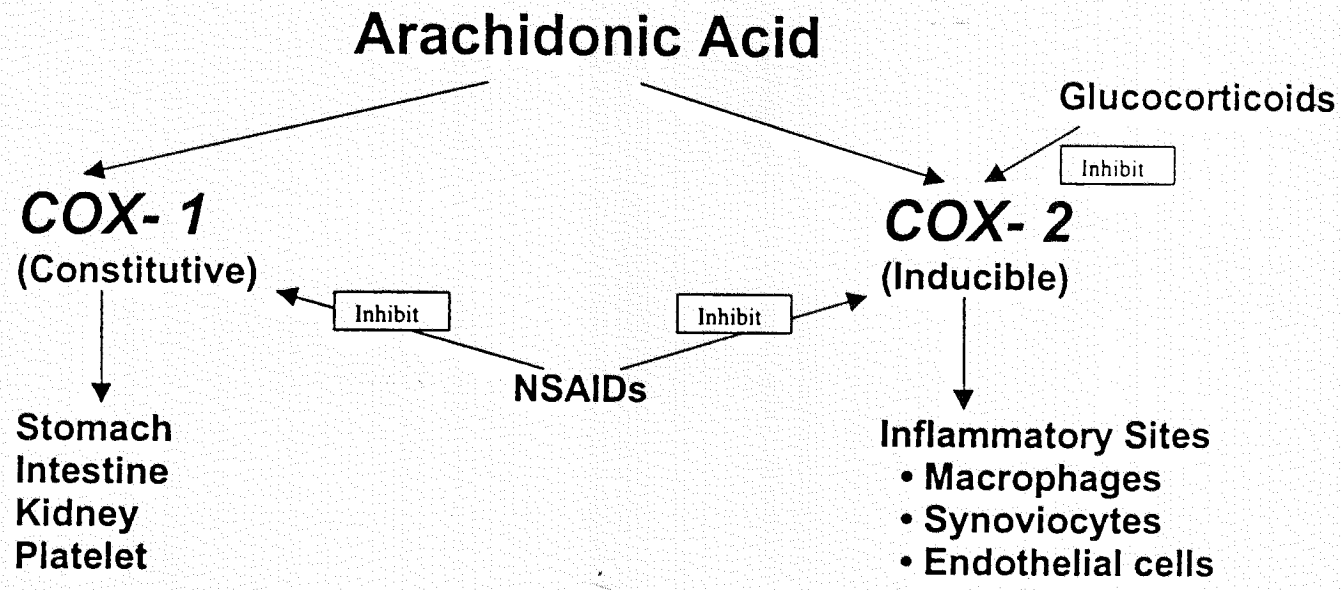
INTRODUCTION:

Currently, the class of agents most commonly used for anti-inflammatory and analgesic conditions is the nonsteroidal anti-inflammatory drugs (NSAIDs). Although the mechanism by which NSAIDs achieve their effect is not completely understood, they are known to inhibit the activity of the enzyme cyclooxygenase (COX), which mediates conversion of arachidonic acid to the prostaglandins that serve as key components of inflammatory processes. However, prostaglandins are also needed to maintain normal gastrointestinal and platelet function, as well as renal function under physiologically stressed conditions. Thus, the anti-inflammatory and analgesic benefits of NSAID therapy are tempered by an increased risk of gastrointestinal ulceration and ulcer complications (such as bleeding, perforation, and gastric outlet obstruction), hemorrhagic diathesis, and nephrotoxicity. Recently, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the gastrointestinal tract, kidney, and platelets. COX-2, a cytokine-inducible enzyme, is normally found in very low amounts in healthy tissue (except the brain and kidney) but is prominently expressed in inflamed tissues. It is particularly noteworthy that COX-2 is not expressed in platelets or the gut. Studies of recombinant enzymes in vitro and in cell lines have demonstrated that as a class, NSAIDs nonselectively inhibit the activity of both COX-1 and COX-2 (figure).

Figure: Roles of COX-1 and COX-2 in Physiologic and Pathophysiologic Functions.



These findings gave rise to the hypothesis that the gastrointestinal, platelet, and renal toxicity of NSAIDs results from inhibition of COX-1, while their therapeutic benefit is a function of inhibition of COX-2. Evidence supporting this hypothesis has been provided by studies showing that:

- COX-2 expression is up-regulated by inflammatory mediators such as cytokines and bacterial endotoxin;
- up-regulation of COX-2 expression is blocked by anti-inflammatory glucocorticoids, which do not alter COX-1 expression; and
- in animals, selective inhibition of COX-2 is anti-inflammatory and analgesic, but cause less gastroduodenal toxicity.

In contrast, NSAIDs, which nonselectively inhibit both COX-1 and COX-2, cause pronounced gastrointestinal toxicity and interfere with platelet function at therapeutic doses.

Rofecoxib is a novel compound that selectively inhibits cyclooxygenase 2 and is being developed as an oral anti-inflammatory and analgesic agent seeking the indications of: the treatment of the signs and symptoms of osteoarthritis (OA), the management of pain and for the treatment of primary dysmenorrhea.

INTEGRATED SUMMARY OF MEDICAL REVIEW - ANALGESIA

Tablets Formulation Development

The manufacturing process and composition of rofecoxib underwent various changes during the development process. The original formulation was designated as Formulation A. After the first few clinical studies, to , the content of the and its addition was moved forward so it would be added to the before the step. This formulation was designated as Formulation B. After the dose range of 12.5 to 50 mg was identified as the likely therapeutic range, it was decided to select a formulation containing active ingredient to to an easier to handle size. This formulation was designated as Formulation C. The composition of the final formulations is the same as that of Formulation C.

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain

Six studies were conducted in patients with postsurgical pain, five in the dental pain model (004, 027, 051, 066, 071) and one in the post orthopedic surgery model (072). Three of these studies are considered to be pivotal (dental pain studies 066 and 071 and post orthopedic surgery study 072).

A summary of these studies is provided in tables 1 and 2.

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain:

Table 1: Post Surgery

Protocol/	Entry Criteria	Treatment Daily Doses (mg)/ Duration
Post-Dental Surgery Pain Studies – Single-Dose		
004 Formulation A	≥18 years, moderate to severe pain post 1 to 2 molars extraction	Rofecoxib 50 mg, 250 mg, 500 mg Ibuprofen 400 mg Placebo
027 Formulation B	≥18 years, moderate to severe pain post ≥2 molars extraction	Rofecoxib 7.5 mg, 25 mg, 50 mg, 100 mg Naproxen NA 550 MG Placebo
051 Formulation C	As Protocol 027	Rofecoxib 12.5 mg, 25 mg, 50 mg Naproxen NA 550 MG Placebo
066 Pivotal Formulation C	≥16 years, moderate to severe pain post ≥2 molars extraction	Rofecoxib 50 mg Ibuprofen 400 mg Placebo
071 Pivotal Formulation C	As Protocol 066	Rofecoxib 50 mg, 100 mg, 200 mg Ibuprofen 400 mg Placebo
Post-Orthopedic Surgery Pain Study – Multiple-Dose		
072 Pivotal Formulation C	≥18 years, moderate to severe pain post-orthopedic surgery	Rofecoxib 50 initial dose-50 subsequent dose 50 initial dose-25 subsequent doses Naproxen 550 initial dose-placebo subsequent doses Placebo

Table 2: Primary Dysmenorrhea Studies

Protocol/	Entry Criteria	Treatment Daily Doses (mg)/ Duration
038 Formulation B	≥18 years, history of moderate to severe primary dysmenorrhea, negative β-hCG	Rofecoxib 50 mg Ibuprofen 400 mg Placebo (Single Dose)
055 Pivotal Formulation C	≥18 years, history of moderate to severe primary dysmenorrhea, negative β-hCG	Rofecoxib 50 initial dose-25 subsequent dose Naproxen 550 Placebo (All for up to 3 days)
056 Pivotal Formulation C	≥18 years, history of moderate to severe primary dysmenorrhea, negative β-hCG	Rofecoxib 50 initial dose-25 subsequent dose 25 initial dose-25 subsequent doses Naproxen 550 Placebo (All for up to 3 days)

Studies Population and Design

Post-Oral Surgery
(Studies # 004, 027, 051, 066 and 071)

All studies, except Protocol 066, were dose-ranging studies of rofecoxib; doses studied ranged from 12.5 to 200 mg with the final formulation C

All protocols used a double-blind (with in-house blinding), randomized, parallel-group study design. Patients met selection criteria at the screening visit. Patients then were required to undergo extraction of ≥2 molars (1 or 2 molars in Protocol 004), at least one of which was partially embedded in bone. Upon development of moderate to severe postsurgical pain, patients consumed a single dose of study medication.

Over the ensuing 24 hours (6 hours for Protocol 004), patients completed the following measures of analgesic efficacy:

1. Completed a diary at various prespecified time points in which they rated pain relief (none, a little, some, a lot, complete), pain intensity (none, slight, moderate, severe), an overall assessment of the study therapy (poor, fair, good, very good, excellent), and the time that rescue medication was taken.
2. Clicked off 1 stopwatch when they achieved meaningful pain relief (only 1 stopwatch in Protocols 004, 027, and 051), or clicked off 2 stopwatches—one when they achieved perceptible pain relief and a second when they achieved meaningful pain relief (2-stopwatch method used in Protocols 066, 071, and 072).

A subset of patients in Protocol 051 had plasma samples obtained at pre-specified time points to assay plasma levels of rofecoxib.

Post-Orthopedic Surgery
(Study # 072)

The purpose of the Post-Orthopedic Surgery Pain Study was to demonstrate both single- and multiple-dose analgesic efficacy for rofecoxib in a analgesic model of more prolonged pain.

Protocol 072 used a double-blind, randomized, parallel-group study design. Patients met selection criteria at the screening visit. Patients then underwent a major orthopedic surgical procedure (total knee replacement, total hip replacement, or fracture repair with open reduction and internal fixation). Postoperatively, patients were treated with narcotics for up to 72 hours. Upon discontinuation of narcotic medication, patients who developed moderate to severe postsurgical pain consumed the first dose of study medication. Epidural or intravenous narcotics must have been discontinued at least 30 minutes prior to dosing and oral or intramuscular narcotics must have been discontinued for at least 4 hours prior to dosing. Over the ensuing 12 hours, patients completed a patient diary analogous to that used in the Post-Dental Surgery Pain Studies and the Primary Dysmenorrhea Studies. Patients also clicked off 2 stopwatches—1 when they achieved perceptible pain relief and a second when they achieved meaningful pain relief (2-stopwatch method). Over the ensuing 5 days, patients received a dose of study medication each morning and completed additional measures of analgesic efficacy including:

1. A record of the date, time, and number of tablets of supplemental analgesic medication consumed each day.
2. A global assessment of study medication each day.
3. A pain intensity rating at three specified time points each day.

Primary Dysmenorrhea Studies
(Studies # 038, 055 and 056)

All protocols used a double-blind (with in-house blinding), randomized, crossover (complete block in Protocols 055 and 056; incomplete block in Protocol 038) study design. Patients met selection criteria at the screening visit. Patients were then provided study medication to take upon development of moderate to severe cramping pain due to dysmenorrhea. Over the ensuing 12 hours (24 hours in Protocol 038), patients completed a diary identical to that described for the Post-Dental Surgery and Post Orthopedic Surgery Pain Studies. A stopwatch was not used to assess onset of analgesia in the Primary Dysmenorrhea Studies. All patient assessments were done from home, but a beeper-paging system was used to remind patients when prespecified postdosing time points occurred.

Protocol 038 was a single-dose study and patients recorded efficacy data for 24 hours after taking study medication. Protocols 055 and 056 were multiple-dose studies. Patients were allowed to take additional doses of study medication every 12 hours as needed; active medication was provided every 12 hours to the naproxen sodium group and every 24 hours to the rofecoxib groups. The time of these additional doses was recorded. In Protocols 055 and 056, patients also compared the different study medications they took during each period and ranked them from best to worst.

Dose-Ranging Studies in Post-Dental Surgery Pain
(Studies # 004, 027 and 051)

During the course of the rofecoxib development program, a variety of doses representing 3 distinct formulations were studied (Table 1).

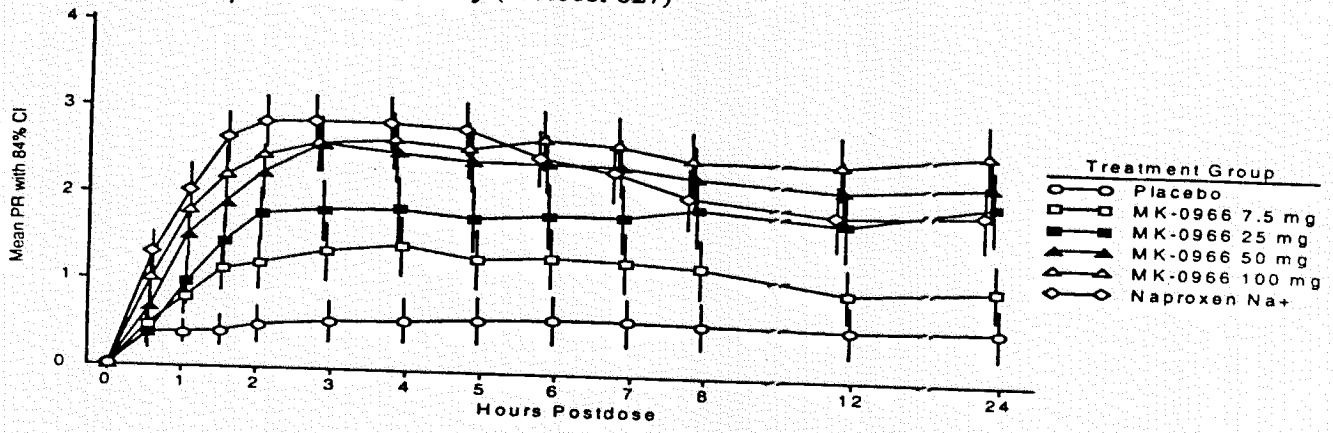
Study 004
The first dose-ranging study (Protocol 004) was a pilot study designed to establish the concept that a COX-2- specific inhibitor has analgesic activity. Doses used in this study were 50, 250, and 500 mg. These doses were chosen because they demonstrated evidence of COX-2 selectivity in [redacted] assays and had been well tolerated in a single-dose healthy-subject study. The drug formulation used in this study (formulation A) was not the final formulation (formulation C).

The results of Protocol 004 demonstrated that all 3 doses of rofecoxib (50, 250, and 500 mg) were more effective than placebo in the treatment of post-dental surgery pain. Significant effects compared with placebo were demonstrated to a similar degree at all doses for all end points, including those characterizing the overall effect, the onset, peak, and duration of analgesia. This analgesic efficacy was comparable to ibuprofen 400 mg, however the study had limited statistical power for comparisons among rofecoxib doses.

Study 027
Protocol 027 compared 7.5, 25, 50, and 100 mg of rofecoxib with placebo and with naproxen Na 550 mg. The drug formulation used in this study (formulation B) was not the final formulation (formulation C). The results of Protocol 027 demonstrated that in the treatment of post-dental surgery pain, rofecoxib administered as a single dose of 7.5, 25, 50, or 100 mg (Figure 1):
(1) was more effective than placebo at the 25-, 50-, and 100-mg doses (the 7.5-mg dose was not significantly distinguishable from placebo on the Patient's Global Evaluation as well as on end points of analgesic onset and duration, indicating that, overall, 7.5 mg is a clinically subeffective dose); (2) exhibited a dose response of efficacy (including onset, peak, and duration of analgesia) with the 7.5- and 25-mg doses generally less effective than the 50-and 100-mg doses; (3) achieved sufficient efficacy at the dose of 50 mg, with some additional efficacy at 100 mg (4) demonstrated comparable efficacy to naproxen at the dose of 100 mg but was statistically inferior compared with naproxen at the dose of 50 mg through the first two hours postdose and at the dose of 25 mg through 6 hours postdose.

Figure 1

Mean Pain Relief (PR) Score' With 84% Confidence Interval by Hours Postdose
(Intention-to-Treat Approach)
Post-Dental Surgery Pain
Phase II Dose-Ranging Study (Protocol 027)



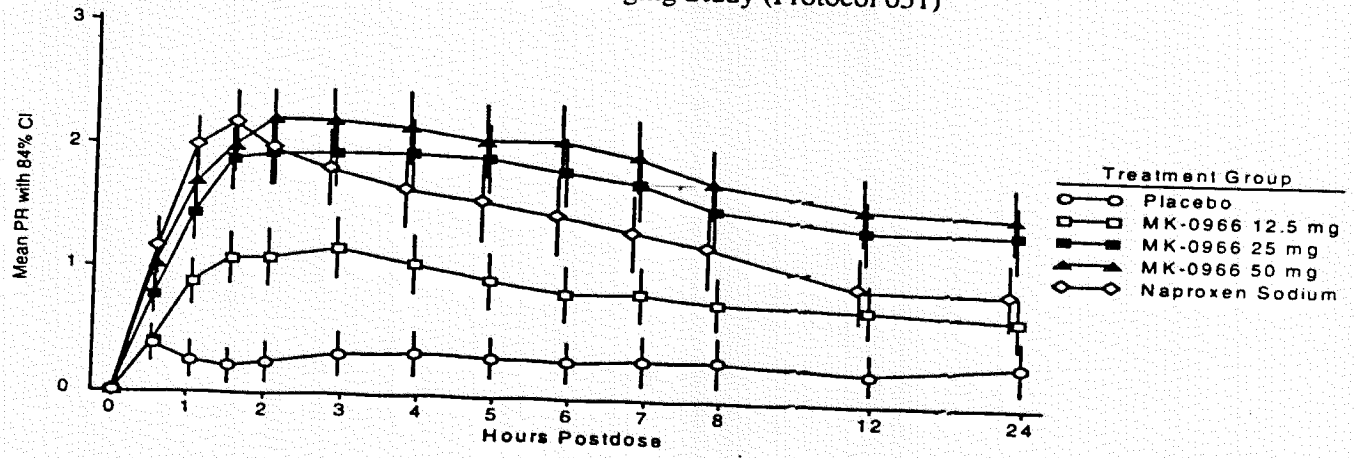
Study 051

Protocol 051 was conducted using 12.5, 25, and 50 mg rofecoxib with all tablets in the final Phase III 12.5% formulation (formulation C).

The results of Protocol 051 demonstrated that rofecoxib administered as a single dose of 12.5, 25, or 50 mg (Figure 2):
(1) was more effective than placebo for all doses; (2) exhibited a dose response of efficacy (including onset, peak, and duration of analgesia) with the 12.5-mg dose generally less effective than the 25- and 50-mg doses and the 50-mg dose generally more effective than the 25-mg dose; (3) achieved minimal clinical efficacy at the 12.5-mg dose; and (4) achieved optimal efficacy at the 50-mg dose.

Figure 2

Mean Pain Relief (PR) Score' With 84% Confidence Interval by Hours Postdose
(Intention-to-Treat Approach)
Post-Dental Surgery Pain
Phase III 12.5% Formulation Dose-Ranging Study (Protocol 051)



Phase III Studies in Post-Dental Surgery Pain
(Studie # 066 and 071)

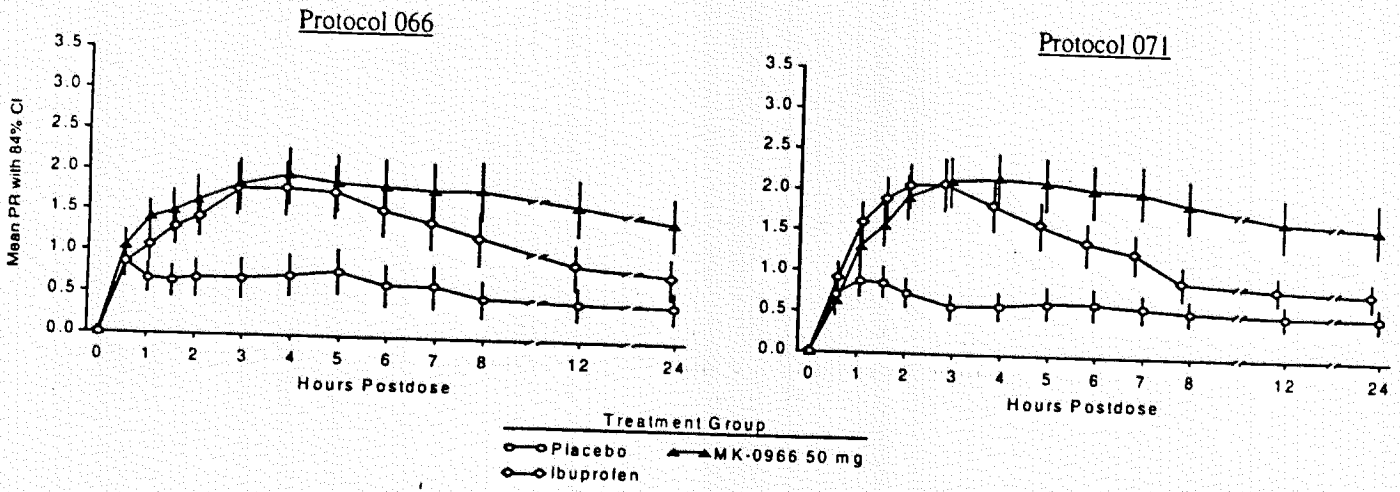
The dose of 50 mg rofecoxib was the minimal dose required to obtain substantial analgesic efficacy (although not necessarily maximal analgesic efficacy) in both Protocols 027 and 051. Thus, 50-mg was chosen as the dose to use in Phase III studies. Protocol 071 also studied 100 and 200 mg of rofecoxib. For additional details to the summary below see the individual study reviews.

Pain Relief Scores

Figure 3 shows a plot of the mean Pain Relief score versus hours postdose. In both studies, the mean Pain Relief scores for 50 mg rofecoxib became significantly greater than placebo at 1 hour postdose and remained significantly better than placebo through to the 24-hour time point by analyzing the data using both last and baseline observation carried forward techniques.

Figure 3

Mean Pain Relief (PR) Score[1] With 84% Confidence Interval by Hours Postdose
(Intention-to-Treat Approach)
Phase III Post-Dental Surgery Pain Studies



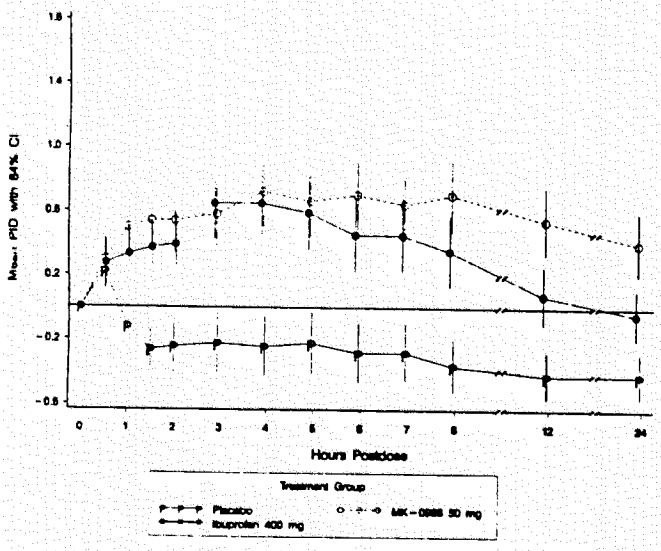
Pain Intensity Scores

The mean PID values for the rofecoxib 50 mg treatment group in both studies (Figure 4) were statistically significantly better than placebo at all assessment times from the 1 hour through 24.0 hours postdose. Reanalyzing the data by using the baseline observation carried forward (BOCF) technique revealed the same results when comparing rofecoxib 50 mg to placebo.

Figure 4

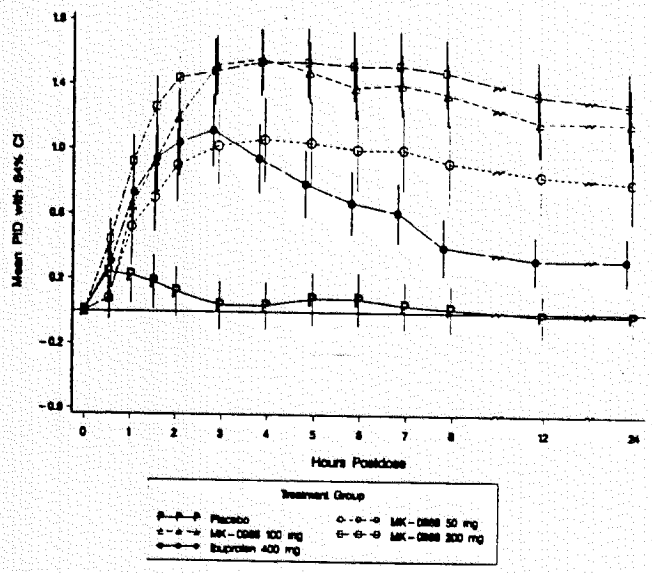
Study 066

Mean Pain Intensity Difference (PID) Score With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach)



Study 071

Mean Pain Intensity Difference (PID) Score With 84% Confidence Interval by Hours Postdose (Intention-to-Treat Approach)



Total of Pain Relief Scores to 8 Hours (TOPAR8)

TOPAR8, was an estimate of the area under the Pain Relief versus Time curve (Figure 3) during the first 8 hours postdose. The LS mean TOPAR8 scores for both Phase III studies are shown in Table 3. In both studies over the 8 hours postdose, rofecoxib 50 mg produced significantly ($p<0.001$) greater LS mean TOPAR8 scores compared with placebo.

Table 3

Effect of Rofecoxib on the End Point of TOPAR8 in Phase III Post-Dental Surgery Pain Studies
(Protocols 066 and 071)

	Protocol 066		Protocol 071	
Parameter	Placebo N= 50	Rofecoxib 50 mg N= 50	Placebo N= 50	Rofecoxib 50 mg N= 50
Baseline Pain Intensity— n (%)				
Moderate	46 (92.0)	46 (92.0)	26 (52.0)	28 (56.0)
Severe	4 (8.0)	4 (8.0)	24 (48.0)	22 (44.0)
Overall Analgesic Efficacy				
TOPAR8 (0 to 32 scale)	LS Mean (95% CI)			
	5.4 (1.8, 8.9)	13.8 (10.2, 17.4)	5.2 (2.8, 7.7)	15.2 (12.7, 17.6)
Difference in TOPAR8 from Placebo	NA	8.5* (4.6, 12.4)	NA	9.9* (6.5, 13.4)
* $p< 0.001$ for difference from placebo.				
NA= Not applicable.				

Sum of Pain Intensity Difference Scores to 8 Hours (SPID8) and Patient's Global Evaluation at 8 Hours

The SPID8 was an estimate of the area under the PID versus time curve (Figure 4) during the 8 hours postdose. At 8 and 24 hours postdose, or at the time the patient took rescue medication, the patient answered the following question in the diary:
"How would you rate the study medication you received for pain?"
"POOR," "FAIR," "GOOD," "VERY GOOD," or "EXCELLENT."

The LS mean scores for these two end points are in Table 4. In both studies, the results from both end points demonstrated that rofecoxib 50 mg produced significantly ($p<0.001$) greater overall analgesic effects compared with placebo. The magnitude of the difference between the rofecoxib group and placebo was generally similar between the studies.