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N-18754-1

NDA

18-754

SBA

Summary Basis of Approval

NDA 18-754

Applicant:
Ives Laboratories Inc.
New York, NY 10017-4073

Drug Generic Name:
Ketoprofen

Drug Trade Name:
Orudis

I. Indications for Use:

Orudis is indicated for use in the treatment of signs and symptoms of the following diseases:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations and indications for use in children have not been established.

II. Dosage Form, Route of Administration and Recommended Dosage:

Orudis is available for oral administration in 50 mg and 75 mg capsules. The recommended daily dose of Orudis is 150 to 300 mg divided in three or four doses. The recommended starting dose is 75 mg three times a day or 50 mg four times a day. If minor side effects appear, they may disappear at a lower dose which may still have an adequate therapeutic effect. If well tolerated but not optimally effective, the dosage may be increased. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well-controlled clinical trials patients on 300 mg did not show greater mean effectiveness. They did, however, show an increased frequency of upper and lower GI distress and headaches. It is of interest that women also had an increased frequency of these adverse effects compared to men. When treating patients with 300 mg a day, the physician should observe sufficient increased clinical benefit to offset potential increased risk. Dosages higher than 300 mg per day are not recommended because they have not been adequately studied. Relatively small people may need smaller doses.

Orudis is rapidly absorbed from the gastrointestinal tract and reaches steady-state plasma concentrations in 24 hours. The absorption is slightly delayed by food but the total bioavailability is not affected. It is recommended that Orudis be taken with or after meals.

III. Manufacturing and Controls:

A. Manufacturing and Control

Satisfactory information is provided for manufacturing and controls of the new drug substance and the drug product.

B. Stability

Data with regard to the drug product support expiration dating for a period of 36 months for the drug product.

C. Methods Validation

An FDA laboratory has confirmed that the analytical methods are adequate for control and regulatory purposes of the new drug substance and the finished drug capsule.

D. Labeling

The "How Supplied" section and "Description" section of the package insert are adequate from a controls viewpoint.

E. Establishment Inspection

Verification was received from Manufacturing Review Branch that states the operations of the facilities involved in the synthesis of the new drug substance and the manufacture of the finished capsules are in compliance with the current Good Manufacturing Practice Regulations and procedures described in this application.

F. Environmental Impact Analysis Report

An EIAR has been submitted and judged to be satisfactory.

IV. Pharmacology

- A. Orudis is a non-steroidal anti-inflammatory agent. Its mode of action is presumed to be through inhibition of prostaglandin synthesis. Its anti-inflammatory activity has been demonstrated by inhibition of carrageenin induced edema in the rat paw. It also protects against ultraviolet light-induced erythema in guinea pigs and reduces the weight of granulomas induced by asbestos or reduces the exudate volume of granulomas induced in cats by croton oil. Analgesic activity was demonstrated by inhibition of phenylbenzoquinone-induced and bradykinin-induced writhing in mice, and by activity in the Randall-Selitto assay. Antipyretic activity was demonstrated by showing decreased hyperthermia in rats from subcutaneous injection of brewer's yeast, and in rabbits, hyperthermia was reduced in response to antigonococcal vaccine injection.

B. Toxicity studies in most animal species showed the gastrointestinal and kidney lesions typical of this class of drugs. There were gastrointestinal ulcerations in rats, dogs, and baboons, and kidney papillary necrosis in mice, rats, and baboons. In addition, the rat kidney also developed tubular degeneration, glomerulonephrosis, and dilated cortical or medullary tubules. Ulcerations, inflammation, necrosis, and fibrosis developed in the rat liver. Anemia developed in the rat, dog, and baboon. At 18 mg/kg/day, spermatogenesis was inhibited in the dog, and testicular regression was observed in rats at 36 mg/kg/day.

A 24 month carcinogenicity study was conducted in C57Bl/6R-P mice at doses of 4, 8, 16, and 32 mg/kg/day p.o. Incidences of tumors were similar in the treated groups and the controls. The 24 month study in Sprague-Dawley rats was terminated early due to poor survival. Although no statistically significant increase in tumor rates above controls was found in the treated rats (doses of 3, 4.5, and 7 mg/kg), the mid-dose group was sacrificed at 92 weeks and the high-dose group at 89 weeks, both with only 17% survival. The female control rats also had relatively poor survival at 24 months: 35% (as compared to a mean of 54% in 7 other studies of Sprague-Dawley rats at the same research facility). For this reason, the sponsor has committed to perform a second carcinogenicity study in another strain of rat.

No mutagenic activity was observed when ketoprofen was tested under the conditions of the Ames mutagenicity assay.

In a study of fertility and general reproductive performance (Segment I) in rats (using doses of 3, 6, and 9 mg/kg/day), the mean number of implantation sites was significantly lower in the mid and high dose groups. The mid dose group also had a significantly lower percentage of pregnancies and a significantly higher number of resorptions when compared to the controls. No effect was observed on the general reproductive function of the male rat.

Teratological studies (Segment II) were done in the mouse (at doses of 3, 6, and 12 mg/kg/day), the rat (at 3, 6, and 9 mg/kg/day), and the rabbit (at 2, 3, 4, 6, and 12 mg/kg/day). No evidence of embryotoxicity was observed in the mouse or the rat. In the rabbit, there was a significant increase in the percentage of resorptions and a significant decrease in the average number of living fetuses in the mid and high dose groups. No teratogenic effects appeared to be related to the administration of ketoprofen.

In the perinatal and post-natal study in the rat (Segment III), delayed or incomplete parturition was seen at 6 and 9 mg/kg and total litter loss occurred in dams of the high dose group.

Peak plasma levels were reached in one half and two hours (2 phases) in the rat, in 1 to 2 hours in the dog, and in 1 hour in the monkey and rabbit. In distribution studies in rats, ketoprofen and its metabolites were found mainly in the intestine, stomach, liver, kidney, plasma, and carcass. Ketoprofen was also found in the milk of lactating dogs. The urine was the major route of excretion for ketoprofen and its metabolites in the rat, dog, rabbit, and monkey. The rat and dog also excreted the drug by way of the bile and feces.

V. Medical:

Ketoprofen is a propionic acid derivative known to inhibit prostaglandin synthesis in vitro and in vivo. Although its mechanism of anti-inflammatory action is unknown, it is presumed to be related to inhibition of prostaglandins.

A. Clinical Pharmacology

Eighteen clinical pharmacology studies involving 235 ketoprofen-treated subjects were performed in the U.S. (Table 1) to study the pharmacokinetics, including bioavailability and metabolism, of ketoprofen alone and co-administered with food, antacid, probenecid, and aspirin; the effect on clinical responses to hydrochlorothiazide, digoxin, and warfarin; the effect on blood coagulation and microscopic gastrointestinal blood loss; the effect of advanced age and of liver impairment on ketoprofen kinetics; and the plasma and synovial fluid kinetics in patients with rheumatoid arthritis.

Ketoprofen caused significantly more microbleeding than placebo but less than aspirin. In addition, as would be expected from a potent prostaglandin synthetase inhibitor, ketoprofen was found to decrease platelet aggregation, release reaction, and adhesion, and to increase bleeding time without affecting other coagulation factors.

Ketoprofen is well-absorbed from the gastrointestinal tract. All formulations (25, 50, 75, and 100 mg) were approximately 90% bioavailable compared to oral solution. Ketoprofen is about 99% protein-bound, mostly to the albumin fraction, and is excreted mainly in the urine (75% to 90% as a glucuronide conjugate). Peak plasma levels (C_{max}) are reached in one-half to two hours after a single dose and are approximately dose-proportional within the range of 75 to 200 mg of ketoprofen. Elimination half-life, the extent of absorption and plasma clearance are not dose-dependent. Steady-state concentrations were as expected,

based on single dose studies, in a 3 day multiple dose study (50 mg q.i.d. for 13 doses), without evidence of further drug accumulation. Terminal half-life averages about 2.5 hours in young volunteers (range 2-4 hours), and is slightly prolonged with advanced age to about 5 hours in elderly volunteers and older patients with rheumatoid arthritis.

Probenecid markedly reduces the plasma clearance of ketoprofen, leading to an increased level of unbound (free) and total ketoprofen which results in approximately a 4 fold increase in unbound ketoprofen concentrations at steady state.

When ketoprofen is coadministered with aspirin the protein binding of ketoprofen is reduced. This is associated with increased plasma levels, AUC and clearance of unbound ketoprofen and with lower plasma levels and AUC of total ketoprofen. Total ketoprofen clearance is increased and the volume of distribution of bound and unbound ketoprofen appears to increase slightly. Aspirin kinetics are unaffected by concurrent ketoprofen treatment.

Food and antacid do not alter the extent of ketoprofen absorption, but food does slow absorption, leading to later (mean time to peak delayed from 1.1 to 2 hours) and decreased peak concentrations (mean peak concentration reduced from 4.1 to 2.4 mg/l).

No significant effects on the pharmacodynamics or kinetics of digoxin, warfarin and hydrochlorothiazide were observed during studies of concomitant treatment with ketoprofen.

A study in 6 healthy male volunteers, age 67-76 years, found that protein binding was decreased in these older patients with increased levels of unbound ketoprofen. Unlike the finding with aspirin, however, renal clearance of free and total ketoprofen was decreased rather than increased. The net effect was higher serum levels and longer half lives (mean 5.6 hours as compared to 2.1 hours in 6 healthy male volunteers, age 21-32). This study suggests that treatment in the elderly should start with decreased doses of ketoprofen.

A study performed in Denmark [Stafanger G., et al.: Pharmacokinetics of ketoprofen in patients with renal impairment. Scand J Rheumatol. 10:189-192, 1981] showed that in patients with renal impairment the terminal half-life of ketoprofen is prolonged, as would be predicted from studies in subjects with normal renal function. A mean half-life of 3.2 hours (based on the ideal fit for a one-compartment model) was found in patients with creatinine clearances of 20-57 ml/min compared to 2.0 hours in younger healthy volunteers.

A study in 8 patients with alcoholic cirrhosis but without overt signs of liver failure did not significantly alter the disposition of ketoprofen. Ketoprofen does not induce hepatic enzymes [Cathcart B.J., et al.: Studies on 2-(3-benzoylphenyl) propionic acid (Orudis). Ann Rheum Dis. 32:62-65, 1973].

In 6 patients with rheumatoid arthritis, synovial fluid levels of ketoprofen reached their peak 2 to 4 hours after oral administration and exceeded the plasma levels between the 4th and 12th hour. The clinical significance of these findings was not studied and is unknown.

Metabolic studies [Populaire P., et al.: Biological behavior: serum levels, excretion and bio-transformation of (benzoyl-3-phenyl)-2-propionic acid or ketoprofen in animals and man. Ann Pharm Fr. 31:735-749, 1973] indicate a biotransformation of ketoprofen, primarily by "acylal" conjugation in the liver, and to a lesser degree, by hydroxylation. The drug is detected in plasma as both the unchanged parent compound and water- and ether-soluble metabolites [Delbarre F., et al.: Pharmacokinetic study of ketoprofen in man using the tritiated compound. Scand J Rheumatol. Suppl. 14:45-52, 1976]; however, no active metabolites have been found.

In the clinical pharmacology studies, most of them single dose studies, ketoprofen was well-tolerated, the principal side effects being the common NSAID gastrointestinal effects.

B. Adequate and Well-Controlled Studies

Several randomized double-blind trials were carried out comparing ketoprofen to either placebo or another active non-steroidal anti-inflammatory drug (NSAID). Of these, 5 were considered to provide adequate evidence of effectiveness for ketoprofen, 2 in rheumatoid arthritis (RA) and 3 in osteoarthritis (OA). In 3 studies (# 306 in RA; #288A and 288AA in OA), two fixed doses of ketoprofen, 200 mg/day and 300 mg/day, were compared to placebo and to each other. Only one study (# 306 in RA) used a pretrial washout period (2 weeks) during which patients were taken off their NSAID therapy before entering the study. All adequate and well-controlled studies excluded the use of other NSAIDs during the course of the trial.

The placebo-controlled and active-controlled trials were analyzed somewhat differently, although the endpoints of interest were the same: physician's and patient's global evaluations (both RA and OA), number of tender joints and number of swollen joints (RA), and joint tenderness and walking pain (OA). These were designated as the "primary efficacy variables".

Statistical analyses for the primary efficacy variables were performed using Week 4 data. For patients who received drug and dropped out before Week 4 (particularly frequent in the placebo-controlled studies), data of the last visit were used. Patients who did not comply with the dose requirement of the study during the 4-week interval were excluded from the analysis (drug consumption was determined by capsule count). Patients were compared with their baseline and changes from baseline calculated. Comparisons to parallel placebo treatment used conventional methods, a significant difference from placebo taken as a 2-tailed p value less than 0.05. In active-controlled studies, in addition to looking for a significant within-group change from baseline, a test was carried out to determine the capacity of the study to detect meaningful differences between ketoprofen and the active control: calculation of the q statistic. The q value is the lower bound on the 95% confidence interval for the ratio of the test drug and control drug treatment effects (each treatment effect defined as the improvement from baseline). Thus, if the effect of the control drug is used as the denominator and the effect of ketoprofen as the numerator of the ratio, the 95% lower bound is a measure of how much less effective, for the particular efficacy parameter, ketoprofen could have been. A low q reflects either a poor response to ketoprofen or poor precision of the study (due to a low N or to high interpatient variability) or both. In general, an active-controlled study is considered persuasively supportive of effectiveness when the q values are at least 0.5 to 0.6 for the major endpoints.

Two-way analysis of variance on "change from baseline" was performed (the statistical model consisted of center main effect, treatment main effect and the center by treatment interactions).

The same data sets were also statistically analyzed by using (1) analysis of covariance (ANOCOVA) and (2) Quade's non-parametric covariance analysis.

The following table summarizes the p and q statistics for all 5 adequate and well-controlled studies. All p values are for comparison of the 2 ketoprofen groups combined against placebo.

<u>Dx</u>	<u>Study</u>	<u>Comparison</u>	<u>Global MD</u>	<u>Variable (at Week 4)</u>		
				<u>Global PT</u>	<u>NTJ</u>	<u>NSJ</u>
RA	306	placebo vs. combined ketoprofen groups (p) 200mg/d vs. 300mg/d	0.024	0.002	0.040	0.64
		ketoprofen groups (q)	0.69	0.68	0.82	0.96
	210	ketoprofen 150-300 mg/d vs. indomethacin 75-150 mg/d (q)	0.70	0.71	0.49	0.90
		<u>Comparison</u>	<u>Global MD</u>	<u>Global PT</u>	<u>Tender- ness</u>	<u>Walk. pain</u>
OA	288A	placebo vs. combined ketoprofen groups (p) 200mg/d vs. 300mg/d	0.004	0.001	0.020	0.009
		ketoprofen groups (q)	0.84	0.88	0.62	0.48
	288AA	placebo vs. combined ketoprofen groups (p) 200mg/d vs. 300mg/d	0.002	0.001	0.014	0.001
		ketoprofen groups (q)	0.88	0.91	0.78	0.67
	289A	ketoprofen 200 mg/d vs. aspirin 2600 mg/d (q)	0.88	0.88	0.73	0.96

Rheumatoid Arthritis

Two studies were considered to provide adequate evidence of ketoprofen's effectiveness in the symptomatic treatment of rheumatoid arthritis. The placebo-controlled study used a fixed dose design: 2 dose levels of ketoprofen vs. placebo. The study comparing ketoprofen to indomethacin allowed titration of the dose of each agent based on patient response.

1. Study 306 (vs. placebo)

A multicenter trial, utilizing a double-blind, parallel design, compared ketoprofen (200 mg/day, N=97, or 300 mg/day, N=93, each given as a q.i.d. regimen) with placebo (N=94). The trial was designed to last 6 weeks. The patients with classical or definite RA were required to meet the ARA criteria of active disease following a pretrial washout of up to 2 weeks. Gold salts, if previously used, were permitted if the regimen remained unchanged. The doses of ketoprofen were not allowed to vary.

The three treatment groups were similar in age (20-77 years, mean 51 years), sex distribution (M 72; F 212), anatomical stage (I+II:221, III+IV:63) and gold therapy (used in 52 of 284 patients, 18%), but the duration of RA was significantly shorter in the placebo group (6.1 years) than in the two ketoprofen groups (8.4 and 7.3 years). The three groups were similar in all analyzed efficacy variables at baseline.

The mean ketoprofen consumption as determined by capsule count was 197 mg/day in the K200 group and 291 mg/day in the K300 group.

Of the total number of 284 enrolled patients, 109 did not complete the 6-week study:

Reason for Dropping Out	No. of Dropouts (%)		
	K200 mg (N=97)	K300 mg (N=93)	Placebo (N=94)
Lack of efficacy	24 (24.7%)	28 (30.1%)	43 (45.7%)
Adverse reactions	3 (3.1%)	3 (3.2%)	3 (3.2%)
Other	1 (1.0%)	2 (2.2%)	2 (2.2%)
Total	28 (28.8%)	33 (35.5%)	48 (51.1%)

The efficacy-analyzable sample comprised 261 patients (K200: N=89, K300: N=87, P: N=85). Using the differences between baseline and Week 4 (or the last visit for dropouts) for 4 standard key variables (Global Assessment by observer and by patient, Number of Tender Joints and Number of Swollen Joints), both doses of ketoprofen combined were found to be superior to placebo except in the Number of Swollen Joints. No difference was detected between the two doses of ketoprofen.

Statistical Test Values (Week 4 vs. baseline data)

	Global Assess. by Observer	Global Assess. by Patient	Number of Tender Joints	Number of Swollen Joints
Keto. vs. pl.	p = 0.024	p = 0.002	p = 0.040	p = 0.64
Keto 200 mg vs. 300 mg	q = 0.69	q = 0.66	q = 0.82	q = 0.96

All p values for within group improvement for ketoprofen at Week 4 vs. baseline were less than 0.001.

Acetaminophen was permitted as a rescue medication during the first week; its consumption was significantly higher in the placebo group than in either ketoprofen group.

There were 3 patients in each treatment group who dropped out due to an adverse reaction. All were due to gastrointestinal disturbances (abdominal pain and/or diarrhea), except for two cases of pruritic rash in the placebo group.

2. Study 210 (vs. indomethacin)

This multicenter, randomized, double-blind, parallel trial compared ketoprofen (n=70) and indomethacin (n=70) in a total of 140 patients (41M, 99F, age 23-82, mean 52 years) with active, definite or classical RA. The study was designed to last 12 weeks. The two groups were similar in their demographic characteristics and clinical symptoms at baseline.

The dosage (q.i.d.) was allowed to vary between 150 and 300 mg/day of ketoprofen (actual mean 233 mg/day) or between 75 and 150 mg/day of indomethacin (actual mean 113 mg/day). Gold salts or antimalarial drugs, if previously used, had to be kept at unaltered doses.

Thirty-four (34) patients out of 140 enrolled in the trial did not complete all visits, as required by the protocol, as follows:

No. of Dropouts (%)

Reason for Dropping Out	Ketoprofen (N=70)	Indomethacin (N=70)
Lack of efficacy	8 (11.4%)	13 (18.6%)
Adverse reactions	8 (11.4%)	4 (5.7%)
Other	0	1 (1.4%)
Total	16 (22.8%)	18 (25.7%)

The efficacy analysis is based on 133 patients (K=66, I=67) after excluding protocol violators.

The analysis of the 4 primary variables showed that the drugs were comparable at Week 4 in 3 out of the 4 primary efficacy variables (Tender Joint Count the exception):

Statistical Test Values (Week 4 vs. Baseline data)

<u>Variable</u>	<u>q values</u>
Global ss. by Investigator	0.70
Global ss. by Patient	0.71
Tender Joint Count	0.49
Swollen Joint Count	0.90

The dropout rates for lack of efficacy were not significantly different.

There were 8 ketoprofen patients and 4 indomethacin patients who dropped out of the study due to adverse reactions, mostly gastrointestinal and CNS disturbances. One patient on ketoprofen had melena without a prior history of GI problems.

Osteoarthritis

The 2 placebo-controlled studies (Study 288A and 288AA) had virtually identical protocols except for a different total duration (4 and 6 weeks, respectively). All 3 studies used a fixed-dose regimen: the placebo-controlled studies compared placebo with 200 and 300 mg/day, the aspirin-controlled study employed a single dose of 200 mg/day ketoprofen vs. 2600 mg/day aspirin. The regimens were all q.i.d.

The primary efficacy variables in OA were Global Assessments by Observer and by Patient, Joint Tenderness, and Walking Pain. The score for Joint Tenderness was calculated as the total pain-on-examination score for all joints (hips and knees) with baseline score divided by the number of joints affected at baseline. Walking Pain rating is based on patient's recollection. Both Joint Tenderness and Walking Pain were rated as none, mild, moderate and severe. The Global Assessments were rated on the same scale at baseline; at the subsequent visits, global assessments were based on changes from baseline, i.e., worded as "marked improvement", "moderate improvement", "minimal improvement", "no change", or "worse". The numerical scale corresponding to these ratings was uniformly shifted to provide a valid basis for the q value analysis.

1. Study 288A (vs. placebo)

This multicenter, randomized, double-blind parallel trial compared ketoprofen (200 mg/day, n=32; or 300 mg/day, n=32) and placebo (n=35) in a total of 99 patients (M 42, F 57, age 40-87, mean 64 years) with osteoarthritis of the hip or knee. The study was designed to last 4 weeks. The treatment groups were similar in their demographic characteristics (except that K300 patients were significantly older, mean 68 years, than the K200 patients, 63 years, or placebo patients, 62 years). The K300 group also had a significantly longer Walking Time at baseline (22.9 vs 19.7 vs. 17.7 sec). These two differences, possibly related to one another, could have influenced the outcome, probably in disfavor of the high-dose ketoprofen group. No baseline differences were seen, however, in the 4 key variables of effectiveness. The hip and knee patients were uniformly distributed among the three groups (approx. 1:2).

The actual mean daily doses were 188 and 288 mg of ketoprofen. After excluding the protocol violators, the K300 group comprised 29 patients, K200 group 30 patients, and the placebo group 30 patients.

Twenty-two patients out of the 99 admitted to the trial did not complete all visits required by the protocol as follows:

Reason for Dropping Out	No. Dropouts (%)		
	K200 mg (N=32)	K300 mg (N=32)	Placebo (N=35)
Lack of efficacy	5 (15.6%)	- 0 -	9 (25.7%)
Adverse reactions	1 (3.1%)	2 (6.3%)	3 (8.6%)
Other	1 (3.1%)	1 (3.1%)	1 (2.9%)
Total	7 (21.8%)	3 (9.4%)	12 (34.3%)

Ketoprofen (both groups combined) was significantly superior to placebo at Week 4 (or last visit for dropouts) in Global Assessments by Observer and by Patient, Walking Pain, and Joint Tenderness. There was no detectable difference between the effectiveness of the two ketoprofen doses. The results are summarized below:

Statistical Test Values (Week 4 vs. baseline data)

<u>Comparison</u>	<u>Global Assess. by Observer</u>	<u>Global Assess. by Patient</u>	<u>Joint Tenderness</u>	<u>Walking Pain</u>
Keto vs. pl.	p = 0.004	p = 0.001	p = 0.020	p = 0.009
Keto 200 mg vs. 300 mg	q = 0.84	q = 0.88	q = 0.62	q = 0.48

The supplementary analyses were generally supportive of the above conclusion. A significant difference between either ketoprofen group and placebo in three types of patient-recalled pain (Morning, Night and Walking Pain) was detected after the first week of treatment. The lack-of-efficacy dropout rate was higher in the placebo group (25.7%) than on ketoprofen 200 mg/day (15.6%) or 300 mg/day (0%). The number of patients rated "markedly" or "moderately" improved was significantly higher in both ketoprofen groups than on placebo (both investigators' and patients' rating).

There were 2 patients on 300 mg ketoprofen, 1 on 200 mg ketoprofen, and 3 on placebo who dropped out due to adverse reaction. The 3 ketoprofen patients all had dyspepsia or epigastric pain. The placebo patients had conjunctivitis, peptic ulcer, and abdominal pain.

2. Study 288 AA (vs. placebo)

The study was conducted according to a multicenter, double-blind, parallel protocol in 202 patients with osteoarthritis of the hip or knee (ketoprofen 300 mg/day n=71, ketoprofen 200 mg/day n=64, and placebo n=67).

Patients were treated with the study medication on a q.i.d. basis for 6 weeks. The three treatment groups were similar in their demographic profile, (M 49, F 153, age 39-90, mean 65 years) and clinical symptoms at baseline.

The actual mean daily doses were 290 mg of ketoprofen (300 mg group) and 191 mg of ketoprofen (200 mg group).

After excluding the protocol violators, the analysis of effectiveness was performed on 125 ketoprofen-treated patients (200 mg/day group, n=57; 300 mg/day group, n=68) and 58 placebo-treated patients.

A total of 90 patients (44.6% of the 202 enrolled patients) failed to complete the 6-week course of double-blind treatment:

Reason for Dropping Out	No. Dropouts (%)		
	K200 mg (N=64)	K300 mg (N=71)	Placebo (N=67)
Lack of efficacy	16* (25%)	15* (21.1%)	29 (43.3)
Adverse reactions	6 (9.4%)	9 (12.7%)	3 (4.5%)
Other	5 (7.8%)	3 (4.2%)	4 (6.0%)
Total	27 (42.2%)	27 (38.0%)	36 (53.8%)

*p less than 0.05 vs. placebo

Ketoprofen (both groups combined) was significantly superior to placebo at Week 4 (or last visit for dropouts) in Global Assessments by Observer and by Patient, in Joint Tenderness and Walking Pain. There was no statistically detectable difference between the effectiveness of the two ketoprofen doses as shown below.

Statistical Test Values (Week 4 vs. baseline data)

Comparison	Global Assess. by Observer	Global Assess. by Patient	Joint Tenderness	Walking Pain
Keto vs. pl.	p = 0.002	p = 0.001	p = 0.014	p = 0.001
Keto 200 mg vs. 300 mg	q = 0.88	q = 0.91	q = 0.78	q = 0.67

The lack-of-efficacy dropout rate was significantly higher in the placebo group (n=29) than in either ketoprofen group (ketoprofen 300 mg, n=15; ketoprofen 200 mg, n=16). The number of patients rated "markedly" or "moderately" improved was significantly higher on ketoprofen 300 mg/day (by patient and observer) and ketoprofen 200 mg/day (by observer) than on placebo.

There were 3 placebo, 6 ketoprofen 200 mg, and 9 ketoprofen 300 mg patients who discontinued due to adverse reaction. These numbers suggest a dose-related trend in those reactions which go beyond the merely annoying. Almost all these reactions in the 2 ketoprofen groups were gastrointestinal disturbances, including one patient on 300 mg/day with gastritis and occult blood in vomitus.

3. Study 289A (vs. aspirin)

This multicenter, randomized, double-blind, parallel trial compared ketoprofen (n=42) and aspirin (n=43) in a total of 85 patients (M 27, F 58, age 35-83, mean 63 years) with osteoarthritis of the hip or knee. The study was designed to last 12 weeks. The treatment groups were similar in their demographic characteristics (joint involvement approx. 1:1) and clinical symptoms at baseline, except that Walking Pain was significantly more severe in the ketoprofen group.

The scheduled daily doses were 200 mg of ketoprofen and 2600 mg of aspirin (actual consumption 190 mg and 2415 mg, respectively).

After excluding the protocol violators, the analysis of effectiveness was performed on 39 ketoprofen and 39 aspirin-treated patients.

Of the 85 patients enrolled, 21 (25%) did not complete the study for the following reasons:

Reason for Dropping Out	No. Dropouts (%)	
	Ketoprofen (N=42)	ASA (N=43)
Lack of efficacy	8 (19.1%)	5 (11.6%)
Adverse reactions	2 (4.8%)	4 (9.3%)
Other	0 (-)	2 (4.7%)
Total	10 (23.9%)	11

Four primary efficacy variables were analyzed to compare therapeutic responses to ketoprofen and aspirin using Week 4 data. The results are summarized below.

<u>Variable</u>	<u>Statistical Test Value</u>
Global Assess. by Observer	q = 0.88
Global Assess. by Patient	q = 0.88
Joint Tenderness	q = 0.73
Walking Pain	q = 0.96

There was no significant difference between the two groups regarding the lack-of-efficacy dropout rate (ketoprofen 19.1% vs. aspirin 11.6%). About two-thirds of patients in each treatment group were classified as improved. The within-treatment improvements in the primary efficacy variables at Week 4 (or earlier for dropouts) were all statistically significant at p less than 0.001 for both treatments.

Two ketoprofen patients and 4 aspirin patients dropped out due to adverse reaction, all but one (aspirin) for gastrointestinal disturbances. One ketoprofen patient dropped out due to peptic ulcer, but he was a 73 year old male with a prior history of peptic ulcer.

C. Supportive Studies

In addition to the 5 studies providing clear evidence of effectiveness, a number of other studies supported the safety and efficacy of ketoprofen in the treatment of rheumatoid arthritis and osteoarthritis but their evidence was less substantial due to problems connected with their design or execution. Their were no adequate and well controlled studies that presented substantial evidence that ketoprofen was ineffective. The supportive studies are summarized in the following table. Although sufficient evidence was not submitted to show the effectiveness of ketoprofen in the treatment of ankylosing spondylitis and acute gouty arthritis, studies in these indications were conducted by the applicant and these studies are also included in the table.

Study # (Indi- cation)	Study Design	Treatment Groups	Dose & Duration	Patients per Group	Dropouts Due to		
					Lack of Efficacy	ADR	Other
201 (RA)	DB,R, P	Keto	100-300 mg/d (mean 246 mg/d) 54 wks	115	38	13	20
		ASA	1800-5400 mg/d (mean 4030 mg/d) 54 wks	114	23	28	18
226 (RA)	DB,R, P (concom. steroids)	Keto	100-300 mg/d (mean 216 mg/d) 24 wks	71	26	2	5
		Placebo	24 wks	74	35	3	5

Study # (Indi- cation)	Study Design	Treatment Groups	Dose & Duration	Patients per Group	Dropouts Due to		
					Lack of Efficacy	ADR	Other
270 (RA)	DB,R, P	Keto	100-300 mg/d (mean 236 mg/d) 24 wks	33	5	0	3
		ASA	1800-5400 mg/d (mean 3530 mg/d) 24 wks	31	4	7	4
182 (RA)	DB,R, P	Keto	150-300 mg/d (mean 225 mg/d) 12 wks	52	5	6	5
		Ibu	1200-2400 mg/d (mean 1717 mg/d) 12 wks	51	7	4	3
275A (OA)	SB,DR	Keto	100-300 mg/d 3 wks	60	0	0	0
297 (AS)	DB,R, X	Keto	200-300 mg/d (mean 245 mg/d) 8 wks	54	4	5	0
		Indo	100-150 mg/d (mean 116 mg/d) 8 wks	52	3	5	2
354 (gout)	DB,R, P	Keto	load: 150 mg + 300 mg/d 7 days	29	0	3	1
		Indo	load: 75 mg + 150 mg/d 7 days	30	1	3	5
298 (gout)	OL	Keto	load: 150 mg + 100-300 mg/d 7 days	20	0	0	2

RA = rheumatoid arthritis, OA = osteoarthritis, AS = ankylosing spondylitis, DB = double-blind, R = randomized, P = parallel, X = crossover, SB = single-blind, DR = dose ranging, OL = open-label, Keto = ketoprofen, Indo = indomethacin, ASA = aspirin, Ibu = ibuprofen.

D. Safety

The overall analysis of adverse reactions (ADRs) was based on a computer-generated grouping of similar or mutually related ADRs into 62 categories classified within 12 COSTART Body Systems. All ADRs were included regardless of the investigator's assessment of relationship to treatment and the database was updated to include ADRs reported after the initial submission of the NDA. An analysis and comparison of ADRs for ketoprofen and other NSAIDs reported to the British Committee on Safety of Medicines (CSM) also was submitted.

Overall incidence of Adverse Reactions

The numbers of patients for each of the ADR categories and their percentages based on the total N=1545 (number of patients in studies longer than 1 week) are presented in Table 4 (first column). The total number of adverse reactions (grouped by category) was 1760. Upper GI Distress (consisting of nausea, dyspepsia, vomiting, epigastric pain, etc., but not peptic ulcer or hematemesis) was the most frequently reported ADR category (29.6% of patients; 26.0% of the ADR entries); it was followed by Headache, CNS Inhibition (somnolence, malaise, depression, etc.) and Lower GI Distress (between 8.4% and 8.7% of patients). Diarrhea was reported by 6.4% of patients; Rash and Renal Functional Impairment each were reported for 4.7% of patients. The categories with fewer than 7 patients have been pooled as "others" by body system.

Pooled prevalence rates for ketoprofen-treated patients (N=978) from the double-blind studies are included in Table 4, 2nd column. The ranking and incidences of ADRs were similar to that of the total population.

Comparative analysis of ADRs by treatment from the double-blind studies is summarized in Table 5. In general, ADRs were similar for ketoprofen and other NSAIDs; compared to aspirin, ketoprofen caused less salicylism, upper GI distress, pruritus, and rash. There were no other significant differences from aspirin, nor any significant differences from ibuprofen or indomethacin. Compared to placebo, ketoprofen was associated with more upper GI distress, lower GI distress and constipation, renal functional impairment, and urinary tract inflammation.

The only statistically significant difference between the ADR incidences in patients receiving ketoprofen 300 mg/day and 200 mg/day (in the fixed-dose trials), was Upper GI Distress, which was more frequent at the higher dose (27% vs. 18% of patients). (See Table 6A) Although not significant, there were also trends of higher incidence at 300 mg/day of headache, stomatitis, lower GI distress, and visual disturbance. Because

of the dose related risk of gastrointestinal distress, coupled with the continuing risk of peptic ulcer throughout treatment with ketoprofen, an attempt should be made to prescribe the lowest effective dose.

As expected, the incidence of ADRs was generally higher in the patients with rheumatoid arthritis, as compared to osteoarthritis.

Upper GI Distress, Headache, Salicylism, Inhibition, Excitation/Nervousness, Rash and Upper Respiratory Inflammations were seen in significantly more RA patients as compared to OA patients (Table 7).

In analyzing the ADRs by duration of treatment (Table 8), the early onset was most prominent for ADRs associated with the pharmacological effect of ketoprofen, a potent cyclo-oxygenase inhibitor, on salt and water excretion. About two-thirds of all reports of Renal Functional Impairment (defined as peripheral or generalized edema or an increase in BUN and/or serum creatinine) and of Weight Increase were made during the first month of ketoprofen therapy.

A similar but less pronounced trend was observed with most other ADR categories, with the exception of Peptic Ulcer and several other ADRs; all of these "other" were observed in less than 1% of patients. Peptic Ulcer and GI Bleeding were almost evenly distributed throughout the treatment. No ADR was identified that would appear to result from a delayed, cumulative effect of long-term ketoprofen therapy.

Among the concomitant medications tested for an interaction with ketoprofen in producing ADRs, the diuretics were clearly involved in the cases of Renal Functional Impairment. Although the diuretic treatment is more often associated with pre-existing serum creatinine or BUN elevations, these baseline abnormalities per se do not predispose to a further deterioration of renal function under ketoprofen treatment.

Other statistically significant differences were plausible but less medically important (thyroid supplements associated with higher rates of CNS symptoms - Inhibition and Excitation - as well as Upper GI Distress; corticosteroids with Upper GI Distress). No unexpected interactions have been detected (see Table 9).

The elderly patients (above 60 years old) did not report any ADR at a rate significantly higher than that for middle-aged (45-60 years old) or younger patients (Table 10). Females had more reports than males in the categories Headache, Upper GI Distress, Diarrhea, and Inhibition (Table 11).

The tally of potentially serious ADRs was based on a medical review of all patients who received ketoprofen, except in single-dose analgesic trials and in clinical pharmacological studies (N=1987). The overwhelming majority of these cases concerned the gastrointestinal system. Peptic Ulcer was detected in 40 ketoprofen-treated patients (2.0%) and GI Bleeding (without an identified ulcer and including cases without objective evidence of a GI lesion) in 14 cases (0.7%). Of the 7 cases of death, none was attributed to ketoprofen, although some contribution of the drug action to the underlying medical problems leading to the fatal outcome cannot be ruled out in 3 patients.

An analysis of liver function test abnormalities involving 944 ketoprofen-treated and 729 control patients are presented in the following table. Only patients with elevations of bilirubin, SGOT/SGPT or alkaline phosphatase 3x the upper limit of normal are included in the table. Patients with lesser elevations of liver function test, i.e., greater than 20% above the upper limit of normal, were common. Such elevations were seen in 2-3% of all patients at baseline, in 6% of placebo-treated patients, in 9% of ketoprofen-treated patients and in 19% of patients treated with aspirin.

Summary of Abnormal Liver Test Findings

	Nml with cont. Rx	Abn with cont. Rx	Pos De- challenge	Unrelated (Pagets)
ketoprofen (N=944)	above 3x 0.7% patients with abnormal test = 7%	0.6%	0.1%	0.1%
aspirin (N=188)	above 3x 1.6% patients with abnormal test = 20%	0.0	1.6%	0.0
placebo (N=364)	above 3x 0.3% patients with abnormal test = 8%	0.5%	0.0	0.0
other/con- trol drugs (N=177)	above 3x 0.0 patients with abnormal test = 2%	0.0	0.0	0.0

As with other nonsteroidal anti-inflammatory drugs there have been rare physician reports of non-fatal cases of hepatitis and jaundice associated with ketoprofen from countries where ketoprofen has been marketed. So far, however, none of the reports have occurred under circumstances in which a definite causal relationship to ketoprofen could be established.

Treatment was discontinued for ADR in 13.1% of patients. The most frequent cause of treatment termination was Upper GI Distress (55% of ADR-related dropouts), followed by Peptic Ulcer (14%) and Lower GI Distress (10%).

As shown in a British report on ketoprofen overdose, acute intake of high doses of ketoprofen (up to 5 g) was tolerated without serious symptoms or clinical consequences in all 20 recorded cases.

The physical examination measures and laboratory values showing statistically significant changes in most of the clinical trials were: increased body weight (1 or 2 pounds on the average), increased BUN (but not creatinine) and reduced hemoglobin and hematocrit. Despite the occurrence of these statistical significant findings indicating a change from baseline values, only in rare cases did the reactions lead to discontinuation of the treatment or cause serious clinical concern.

Published data on tolerance of ketoprofen treatment are available for a total of 10,824 foreign patients. The dose of ketoprofen used in these studies was usually between 100 and 200 mg per day. Despite differences between controlled and uncontrolled arthritis trials, the statistics on adverse reactions are similar: about 19% of ketoprofen-treated patients reported ADR (n=1,992) and only 4-6% discontinued treatment for this reason. The gastrointestinal tract accounted for most of the side effects with the neurological/sensory organ system and skin involved to a much lesser extent. Table 12 which lists the individual ADR by organ system, depicts very generally the types of ADR reported by approximately 11,000 patients in clinical experience since 1972. The table lists a total of 2,305 occurrences of side effects of which 71% are in the gastrointestinal system, 11% in the neurological/sensory system, and 7% in the skin system accounting for 97% of the total ADR. No particular unusual or untoward adverse reaction was reported. The most severe reported gastrointestinal problems were peptic ulcer (n=16, 0.15%) and hematemesis or melena (n=11, 0.10%).

Postmarketing surveillance data were obtained from France, the United Kingdom, Canada, West Germany, Japan, Switzerland and Belgium. In accordance with the results of U.S. and foreign clinical studies, most of the reports concern gastrointestinal system. Renal ADRs, anaphylaxis, hepatitis, and hematopoietic disorders were rare.

VI. Approved Package Insert:

A copy of the current approved package insert is attached.

Attachments: Tables 1 through 12 (note: there are no tables 2 and 3)

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Orudis: Summary Basis of
Approval

INDUCTION 12/20/85

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TABLE 1
Summary of Clinical Pharmacology Studies Performed in the U.S.

MDS # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
280 (1.5)	R. Williams San Francisco, CA	1) Relative bio- availability of 2 50 mg formulations	Open, randomized 2-way crossover	12	12	0	Single dose of: 1) K 50 mg - IND capsule formulation 2) K 50 mg - capsule without excipients or 3) K 50 mg solution (1 week washout between treatments) K 50 mg (13 doses) QID
		2) multiple dose kinetics of K 50 mg	Open	6	6	0	All formulations bioequivalent and approx 100% bioavailable. No accumulation after multiple dosing
309 (1.7)	J. Arnold Kansas City, MO	Interaction with warfarin (vs. placebo)	Double-blind, randomized, parallel	28 (14 on K) (14 on PBO)	28	0	12-day warfarin (7.5 mg) stabilization 7-day K 50 mg QID or placebo and warfarin 7.5 mg 3-day drug-free washout
							No change in PT. -No clinical interaction with warfarin observed during concomitant treatment with K.

K = Ketoprofen PBO = placebo ASA = aspirin

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TABLE I
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MDS # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
315 (1.54)	C. Mielke San Francisco, CA	Evaluation of hemostasis (vs placebo)	Double-blind, randomized, parallel	30 (21 on K) (9 on PBO)	10	20	24 days - K 50 mg QID or placebo K decreased platelet aggregation, release reaction and adhesion. K increased bleeding time without affecting other coagulation parameters.
316 (1.7)	G. Lewis Boston, MA	Interaction with digoxin	Open	12	9	3	Day 1-4 - digoxin alone (individualized dose) Day 5-8 - K 50 mg QID + digoxin (individual- ualized dose) Day 9 - digoxin alone (individualized dose) No interaction with digoxin observed during concomitant treatment with K.

K = Ketoprofen PBO = placebo

TABLE I
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MDS # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
319 (1.8)	G. Lewis Boston, MA	Interaction with hydrochlorothiazide	Open	12	8	4	Day 1-4 - HCTZ alone (individualized dose) Day 5-8 - K 50 mg QID + HCTZ (individualized dose) Day 9 - HCTZ alone (individualized dose) No clinical interaction was observed between HCTZ and K.
320 (1.9)	B. Bivins Lexington, KY	Interaction with food & antacid	Open, randomized, 3-way crossover	12	12	0	Single dose K 50 mg alone, with standard breakfast or with 30 ml Maalox® (1 week washout between treatments) -No interaction with antacid or food for AUC, however, C _{max} decreased and T _{max} increased with food.
322 (1.6)	B. Bivins Lexington, KY	Dose proportionality, pharmacokinetics & safety of K 50 75, 150 & 300 mg	Open, single ascending dose	12	12	0	Single dose of K 50 mg, 75 mg, 150 mg & 300 mg (1 week washout between doses) K is linear for AUC between 75 and 300 mg doses
323 (1.4)	R. Williams San Francisco, CA	Interaction with probenecid	Open, randomized 3-way crossover	6	6	0	K 50 mg QID alone for 13 doses or K 50 mg QID for 13 doses + 500 mg probenecid for 16 doses (1 week washout between treatments) Probenecid significantly increased the kinetics of unbound (or active) K.
K = ketoprofen				HCTZ = hydrochlorothiazide			C _{max} = max. plasma conc. T _{max} = time to max. conc.

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TABLE I
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MDS # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
324 (1.54)	J. Arnold Kansas City, MO	Evaluation of GI microbleeding (vs. ASA)	Single-blind, placebo period & double-blind, parallel, active treatment	14	14	0	Day 1-7 - placebo QID Day 8-14 - K 50 mg QID or ASA 975 mg QID Day 15-20 - placebo QID Average blood loss was significantly lower (50%) with K than that observed with ASA.
326 (1.9)	R. Williams San Francisco, CA	Interaction with ASA (effects of ASA on pharmacokinetics of K)	Open, randomized 2-way crossover	6	6	0	K 50 mg QID alone for 13 doses or K 50 mg QID for 13 doses + ASA 975 mg QID for 16 doses (1 month washout between treatments) ASA did not affect the kinetics of unbound (or active) K.

ASA = aspirin K = ketoprofen

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TABLE I
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MD5 # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
327 (1.9)	R. Williams San Francisco, CA	Interaction with ASA Effects of K on phar- macokinetics of ASA	Open, randomized, 2-way crossover	8	8	0	ASA 975 mg QID alone for 25 doses or ASA 975 mg QID for 25 doses + K 50 mg QID for 32 doses (1 month washout between treatments) K did not alter the kinetics of ASA.
330 (1.5)	B. Bivins Lexington, KY	Relative bioavail- ability of K 75 mg & K 25 mg (x 3)	Open, randomized, 3-way crossover	18	18	0	Single dose of: 1) K 25 mg capsules x 3 2) K 75 mg capsules 3) K 75 mg solution All formulations are bioequivalent and approx. 100% bioavailable for AUC.
387 (1.5)	B. Bivins Lexington, KY	Relative bioavail- ability of K 100 mg & K 50 mg (x2)	Open, randomized, 3-way crossover	12	12	0	Single dose of: 1) K 50 mg capsules x 2 2) K 100 mg capsules 3) K 100 mg solution (1-week washout between treatments) All formulations are bioequivalent and approx. 100% bioavailable for AUC.

ASA = aspirin

K = ketoprofen

AUC = area under the plasma conc. time curve

TABLE 1
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MDS # VOL.	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
444* (1.4)	R. Williams San Francisco, CA	To compare the pharmacokinetic profile of a single 100 mg capsule dose of ketoprofen in healthy elderly and young adult volunteers	Open-label, single dose	12	12	0	Six healthy elderly (mean age = 73.3 ± 3.4 yrs) and six healthy adult young male volunteers (mean age = 27.2 ± 2.5 yrs) received a single oral dose of ketoprofen (100 mg). Results indicate that total bioavailability and the active free fraction of ketoprofen are slightly increased while plasma and renal clearance and protein binding are reduced in the elderly. This may be attributable to a lower plasma albumin and normal physiological reduction in renal and hepatic function seen with age.
457* (1.5)	R. Williams San Francisco, CA	To compare the pharmacokinetic profile of a single oral dose (100 mg capsule) of ketoprofen in patients with stable, compensated cirrhosis and normal volunteers.	Open-label, single dose	16	16	0	Eight normal volunteers and eight cirrhotic patients demonstrated similar pharmacokinetics after single dosing with ketoprofen, 100 mg. The only significant difference showed that unbound ketoprofen increased 1.35 times in cirrhotics over control. Alcoholic cirrhosis does not significantly alter the disposition of ketoprofen.

*submitted to NDA 19-397 (Analgesic indication)

TABLE 1
Summary of Clinical Pharmacology Studies Performed in the U.S.
(Continued)

MDS # VOL	INVESTIGATOR/CENTER	OBJECTIVE	DESIGN	NUMBER OF COMPLETED SUBJECTS/PATIENTS			DRUG REGIMEN/RESULTS
				Total	Male	Female	
471* (1.6)	R. Williams San Francisco, CA	To assess the relative bioavailability and bioequivalency of a single dose of Titrados® tablets 25 mg x 4, Titrados® tablets 100 mg x 1, 100 mg oral solution, and 100 mg x 1 capsule formulation	(Open-label, randomized, single dose four-way crossover (7-day washout between dosing))	24	12	12	The three single doses of ketoprofen (25 mg x 4 Titrados® tablets, 100 mg x 1 Titrados® tablet, and 100 mg x 1 Orudis® capsule) were approximately 100% bio-equivalent. In addition, the three formulations were relatively 100% bio-available when compared to a solution.
480	W. J. Blechman Hollywood, FL	To assess the pharmacokinetic profile of ketoprofen in the plasma and synovial fluid of patients with rheumatoid arthritis following a single oral dose of a 100 mg ketoprofen capsule and multiple doses of 100 mg ketoprofen capsules given tid for 5 days (13 doses)	Open-label, single- and multiple-dose	6	4	2	Ketoprofen did not accumulate in the plasma or synovial fluid upon multiple dosing (100 mg tid) in adult rheumatoid arthritic patients and a significant amount of ketoprofen can be detected in the synovial fluid.
498* (1.7)	R. Williams San Francisco, CA	To assess the relative bioavailability and bioequivalency of the ketoprofen, 25 mg capsule (x 2), 50 mg capsule (x 1) and 50 mg oral solution	(Open-label, randomized, single dose, three-way crossover (7-day washout between dosing))	18	9	9	Eighteen normal volunteers received a single dose of ketoprofen; 25 mg (x 2) capsules, 50 mg (x 1) capsules and a 50 mg oral solution. The two capsule formulations were approximately 100% bioavailable as compared to the solution and 100% bioequivalent.

*submitted to NDA 19-397 (analgesic indication)

TABLE 4

Prevalence of grouped ADRs in
ketoprofen-treated patients:

- a) total population (N=1545)
b) double-blind studies (N=978)

ADR Category	Total		Double-Blind	
	n	% of 1545	n	% of 978
Upper GI Distress	457	29.6%	252	25.8%
Headache	134	8.7%	92	9.4%
Inhibition	131	8.5%	68	7.0%
Lower GI Distress	130	8.4%	58	5.9%
Diarrhea	99	6.4%	58	5.9%
Rash	73	4.7%	28	2.9%
Renal Function Impairment	73	4.7%	36	3.7%
Constipation	66	4.3%	34	3.5%
Salicylism	56	3.6%	24	2.5%
Visual Disorders	46	3.0%	24	2.5%
Excitation/Nervousness	46	3.0%	26	2.7%
Peptic Ulcer	38	2.5%	3*	0.3%
Oral Inflammation	26	1.7%	11	1.1%
Upper Respiratory Inflammation	27	1.8%	8	0.8%
Pruritus	24	1.6%	9	0.9%
Myalgia	23	1.5%	5*	0.5%
Micturition Disorders	23	1.5%	14	1.4%
External Eye Disorders	21	1.4%	12	1.2%
Rhythm Disturbances	21	1.3%	6*	0.6%
Urinary Tract Inflammation	19	1.2%	9	0.9%
Allergic Reactions	18	1.2%	8	0.8%
Other Oral Symptoms	14	0.9%	7	0.7%
Coagulation Disorders	12	0.8%	6	0.6%
Genital Bleeding	11	0.8%	4	0.4%

* included as "other" in the tally of double-blind trials (Vol. 9.2, p. 55)

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TABLE 4
(continued)Prevalence of grouped ADRs in
ketoprofen-treated patients:a) total population (N=1545)
b) double-blind studies (N=978)

ADR Category	Total		Double-Blind	
	n	% of 1545	n	% of 978
Hypertension	9	0.6%	3	0.3%
Anemia	9	0.6%	0	-
Tactile Disorders	9	0.6%	0	-
Weight Increase	9	0.6%	8	0.8%
Bronchopulmonary Disorders	9	0.6%	3	0.3%
Fever/Chills	8	0.5%	6	0.6%
GI Bleeding	8	0.5%	3	0.3%
Back Pain	8	0.5%	1	0.1%
Skin Infections	8	0.5%	3	0.3%
Vasodilation	7	0.5%	7	0.7%
Balance Disorders	7	0.5%	2	0.2%
Seborrhea	7	0.5%	0	-
Taste Disorders	7	0.5%	5	0.5%
Other*: Body as a Whole	5	0.3%	9	0.9%
Cardiovascular	16	1.0%	11	1.1%
Digestive	11	0.7%	14	1.4%
Endocrine	1	0.1%	0	-
Hemic/Lymphatic	1	0.1%	6	0.6%
Metabolic/Nutritional	6	0.4%	2	0.2%
Musculoskeletal	0	-	6	0.6%
Nervous	4	0.3%	5	0.5%
Respiratory	4	0.3%	4	0.4%
Skin & Appendages	21	1.4%	10	1.0%
Special Senses	3	0.2%	5	0.5%
Urogenital	6	0.4%	8	0.8%

*ADRs with frequencies of 1-6 are pooled under "other"; the figures for "other" are sums of patient/category entries rather than numbers of patients.

Table 5
Comparative analysis of ADRs by treatment
(double-blind studies)

ADR CATEGORY	Ketoprofen N=521	Placebo N=319	Ketoprofen N=233	ASA N=228	Ketoprofen N=176	Indomethacin N=181	Ketoprofen N=86	Ibuprofen N=80
I. BODY AS A WHOLE								
FEVER/CHILLS	4 (0.8%)	1 (0.3%)	0	1 (0.4%)	2 (1.1%)	0	0	0
LE SYNDROME	0	0	0	0	0	0	0	0
ALLERGIC REACTIONS	2 (0.4%)	2 (0.6%)	4 (1.7%)	6 (2.6%)	2 (1.1%)	1 (0.6%)	0	0
PAIN	0	0	2 (0.9%)	0	0	0	0	0
HEADACHE	28 (5.4%)	20 (6.3%)	19 (8.2%)	18 (7.9%)	29 (16.5%)	45 (24.9%)	16 (18.6%)	15 (18.8%)
SALICYLISM	3 (0.6%)	4 (1.3%)	17 (7.3%)	70 (30.7%)	4 (2.3%)	7 (3.9%)	0	2 (2.5%)
II. CARDIOVASCULAR								
RHYTHM DISTURBANCES	1 (0.2%)	0	3 (1.3%)	3 (1.3%)	2 (1.1%)	0	0	0
CORONARY ISCHEMIA	1 (0.2%)	0	0	1 (0.4%)	0	0	0	0
HYPERTENSION	1 (0.2%)	0	1 (0.4%)	2 (0.9%)	1 (0.6%)	1 (0.6%)	0	0
VENOUS DISORDERS	0	0	1 (0.4%)	0	0	0	0	0
CARDIAC INSUFFICIENCY*	0	0	0	1 (0.4%)	0	0	0	0

A total of 1766 patients (92% on ketoprofen)

A total of 1766 patients (978 on ketoprofen and 788 on control drugs) from 21 double-blind studies (11 parallel studies and 10 crossover studies) are included. AUM data from the first treatment period of the 8 crossover studies are not included. The 12 patients who received ketoprofen during the first treatment period in study 10011 (three-way crossover study: ketoprofen, ibuprofen and placebo) are included twice (in ketoprofen vs. placebo and in ketoprofen vs. ibuprofen). Similarly the 9 patients who received ketoprofen during the first treatment period 1 in study 10012 (ketoprofen vs. ASA vs. placebo) are also counted twice. Statistical significance was assessed by the Wilcoxon test.

*** $p < 0.001$

*** $p < 0.001$

✱
✱

• $p < 0.05$

TABLE 5 (continued)
Comparative analysis of ADRs by treatment
(double-blind studies)

ADR CATEGORY	Ketoprofen N=521	Placebo N=319	Ketoprofen N=733	A.A. N=228	Ketoprofen N=176	Indomethacin N=181	Ketoprofen N=86	Ibuprofen N=80
II. <u>CARDIOVASCULAR (cont'd)</u>								
<u>VASODILATION</u>	2 (0.4%)	1 (0.3%)	4 (1.7%)	5 (2.2%)	0	0	1 (1.2%)	0
PERIPHERAL ISCHEMIA	0	0	0	0	1 (0.6%)	0	0	0
III. <u>DIGESTIVE</u>								
<u>INCREASED APPETITE</u>	1 (0.2%)	2 (0.6%)	0	0	0	0	0	0
<u>ORAL INFLAMMATION</u>	1 (0.2%)	0	8 (3.4%)	5 (2.2%)	1 (0.6%)	1 (0.6%)	1 (1.2%)	1 (1.3%)
<u>OTHER ORAL SYMPTOMS</u>	3 (0.6%)	3 (0.9%)	3 (1.3%)	5 (2.2%)	1 (0.6%)	2 (1.1%)	0	0
<u>UPPER GI DISTRESS</u>	114 (21.9%)**	42 (13.2%)	64 (27.5%)**	95 (41.7%)	46 (26.1%)	34 (18.8%)	28 (32.6%)	31 (38.8%)
<u>LOWER GI DISTRESS</u>	26 (5.0%)*	5 (1.6%)	18 (7.7%)	21 (9.2%)	10 (5.7%)	6 (3.3%)	4 (4.7%)	3 (3.8%)
<u>DIARRHEA</u>	24 (4.6%)	25 (7.8%)	13 (5.6%)	12 (5.3%)	12 (6.8%)	19 (10.5%)	9 (10.5%)	7 (8.8%)
<u>CONSTIPATION</u>	14 (2.7%)*	1 (0.3%)	5 (2.1%)	13 (5.7%)	11 (6.3%)	5 (2.8%)	4 (4.7%)	0
<u>PEPTIC ULCER</u>	2 (0.4%)	1 (0.3%)	1 (0.4%)*	5 (2.2%)	0	1 (0.6%)	0	0
<u>GI BLEEDING</u>	1 (0.2%)	0	1 (0.1%)	0	1 (0.6%)	0	0	0
<u>LIVER FUNCTIONAL IMPAIRMENT</u>	0	1 (0.3%)	0	2 (0.9%)	0	0	0	0
<u>BILIARY DISORDERS</u>	0	0	0	0	0	0	0	0
IV. <u>ENDOCRINE</u>								
<u>THYROID DISORDERS</u>	0	0	0	0	0	0	0	0

** p<0.01

* p<0.05

TABLE 5 (continued)
Comparative analysis of ADRs by treatment
(double-blind studies)

ADR CATEGORY	Ketoprofen N=521	Placebo N=319	Ketoprofen N=333	ASA N=228	Ketoprofen N=176	Indomethacin N=181	Ketoprofen N=86	Ibuprofen N=80
<u>V. HEMIC AND LYMPHATIC</u>								
LEUKOPENIA	0	0	0	0	0	0	0	0
ANEMIA	0	0	0	0	0	0	0	0
COAGULATION DISORDERS	0	0	5 (1.5%)	3 (1.3%)	0	1 (0.6%)	0	0
<u>VI. METABOLIC AND NUTRITIONAL</u>								
WEIGHT DECREASE	0	0	0	0	0	0	0	0
WEIGHT INCREASE	1 (0.2%)	0	0	7 (3.1%)	7 (4.0%)	2 (1.1%)	0	0
THIRST	2 (0.4%)	0	0	0	0	0	0	0
<u>VII. MUSCULOSKELETAL</u>								
PAIN, BACK	1 (0.2%)	2 (0.6%)	0	2 (0.9%)	0	1 (0.6%)	0	0
MYALGIA	0	2 (0.6%)	4 (1.2%)	5 (2.2%)	1 (0.6%)	1 (0.6%)	0	1 (1.3%)
<u>VIII. NERVOUS</u>								
PSYCHOTIC DISORDERS	0	1 (0.3%)	0	1 (0.4%)	0	0	0	0
NEUROMUSCULAR DISORDERS	0	0	0	0	0	0	0	0
TACTILE DISORDERS	0	0	3 (1.3%)	1 (0.4%)	0	1 (0.6%)	0	2 (2.5%)

TABLE 5 (continued)
Comparative analysis of ADRs by treatment
(double-blind studies, I)

ADR CATEGORY	Ketoprofen N=521	Placebo N=319	Ketoprofen N=233	A/A N=228	Ketoprofen N=176	Indomethacin N=181	Ketoprofen N=86	Ibuprofen N=80
VIII. NERVOUS (cont'd)								
INHIBITION	20 (3.8%)	10 (3.1%)	19 (8.2%)	11 (13.6%)	20 (11.4%)	22 (12.2%)	9 (10.5%)	16 (20.0%)
EXCITATION/								
NERVOUSNESS	9 (1.7%)	5 (1.6%)	9 (3.9%)	6 (2.6%)	6 (3.4%)	14 (7.7%)	2 (2.3%)	5 (6.3%)
BALANCE DISORDERS	2 (0.4%)	0	0	1 (0.4%)	0	1 (0.6%)	0	1 (1.3%)
IX. RESPIRATORY								
RESPIRATORY BLEEDING	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
UPPER RESPIRATORY								
INFLAMMATION	4 (0.8%)	1 (0.3%)	2 (0.9%)	11 (4.8%)	1 (0.6%)	2 (1.1%)	1 (1.2%)	3 (3.8%)
BRONCHOPULMONARY								
DISORDERS	0	0	2 (0.9%)	2 (0.9%)	1 (0.6%)	0	0	0
X. SKIN AND APPENDAGES								
PRURITUS	3 (0.6%) *	8 (2.5%)	3 (1.3%) *	13 (5.7%)	2 (1.1%)	3 (1.7%)	1 (1.2%)	2 (2.5%)
SWEATING	1 (0.2%)	1 (0.3%)	2 (0.9%)	2 (0.9%)	0	1 (0.6%)	1 (1.2%)	0
SEBORRHEA	0	0	0	0	0	0	0	1 (1.3%)
DRY SKIN	0	0	0	0	1 (0.6%)	1 (0.6%)	0	0
PIGMENTATION								
DISORDERS	0	0	0	1 (0.4%)	0	1 (0.6%)	0	0
HAIR DISORDERS	0	2 (0.6%)	0	1 (0.4%)	1 (0.6%)	4 (2.2%)	0	0
HEALING DELAYED	0	0	1 (0.4%)	0	0	0	0	0
NAIL DISORDERS	0	0	0	2 (0.9%)	0	0	0	0

* p<0.05

TABLE 5 (continued)
Comparative analysis of ADRs by treatment
(double-blind studies, 1)

ADR CATEGORY	Ketoprofen N=521	Placebo N=319	Ketoprofen N=233	ASA N=228	Ketoprofen N=176	Indomethacin N=181	Ketoprofen N=86	Ibuprofen N=80
X. SKIN AND APPENDAGES (Cont'd)								
SKIN INFECTIONS	1 (0.2%)	0	1 (0.4%)	3 (1.3%)	0	0	1 (1.2%)	0
RASH	13 (2.5%)	11 (3.5%)	9 (3.9%)	21 (9.2%)	4 (2.3%)	5 (2.8%)	2 (2.3%)	5 (6.3%)
XI. SPECIAL SENSES								
SMELL DISORDERS	0	0	0	0	0	0	0	0
PAIN, EAR	0	0	0	1 (0.4%)	0	1 (0.6%)	0	0
VISUAL DISORDERS	5 (1.0%)	3 (0.9%)	8 (3.4%)	10 (4.4%)	9 (5.1%)	3 (1.7%)	2 (2.3%)	7 (8.8%)
EXTERNAL EYE								
DISORDERS	1 (0.2%)	3 (0.9%)	7 (3.0%)	5 (2.2%)	4 (2.3%)	2 (1.1%)	0	0
TASTE DISORDERS	2 (0.4%)	0	1 (0.4%)	2 (0.9%)	2 (1.1%)	0	0	0
XII. UROGENITAL								
MICTURITION								
DISORDERS	4 (0.8%)	3 (0.9%)	4 (1.7%)	1 (0.4%)	6 (3.4%)	0	0	0
URINARY TRACT								
INFLAMMATION	6 (1.2%)	0	3 (1.3%)	2 (0.9%)	0	0	0	0
GENITAL BLEEDING	1 (0.2%)	0	1 (0.4%)	0	1 (0.6%)	0	2 (2.3%)	1 (1.3%)
OTHER GENITAL								
SYMPTOMS	0	0	0	1 (0.4%)	1 (0.6%)	2 (1.1%)	0	0
RENAL FUNCTIONAL								
IMPAIRMENT	8 (1.5%)	1 (0.3%)	13 (5.6%)	6 (2.6%)	7 (4.0%)	5 (2.8%)	8 (9.3%)	5 (6.3%)

* p<0.05

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TABLE 6A

Analysis of ADRs by dose in the fixed-dose trials
(Studies 288A, 288AA and 306): No. of Patients (%)

ADR CATEGORY	Daily Dose (by Assignment)	
	200 mg (N=193)	300 mg (N=196)
I. <u>BODY AS A WHOLE</u>		
FEVER/CHILLS	0	1 (0.5%)
ALLERGIC REACTIONS	4 (2.1%)	4 (2.0%)
HEADACHE	8 (4.2%)	13 (6.6%)
SALICYLISM	1 (0.5%)	1 (0.5%)
II. <u>CARDIOVASCULAR</u>		
CORONARY ISCHEMIA	0	1 (0.5%)
HYPERTENSION	0	1 (0.5%)
III. <u>DIGESTIVE</u>		
INCREASED APPETITE	1 (0.5%)	0
ORAL INFLAMMATION	1 (0.5%)	0
OTHER ORAL SYMPTOMS	0	3 (1.5%)
UPPER GI DISTRESS	35 (18.1%)	53 (27.0%)
LOWER GI DISTRESS	7 (3.6%)	14 (7.1%)
DIARRHEA	10 (5.2%)	8 (4.1%)
CONSTIPATION	5 (2.6%)	6 (3.1%)
VI. <u>METABOLIC AND NUTRITIONAL</u>		
WEIGHT INCREASE	0	1 (0.5%)
THIRST	1 (0.5%)	1 (0.5%)
VII. <u>MUSCULOSKELETAL</u>		
PAIN, BACK	0	1 (0.5%)
VIII. <u>NERVOUS</u>		
INHIBITION	6 (3.1%)	8 (4.1%)
EXCITATION/NERVOUSNESS	4 (2.1%)	4 (2.0%)
IX. <u>RESPIRATORY</u>		
UPPER RESP. INFLAMMATION	1 (0.5%)	0

* p<0.05

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TABLE 6A
(continued)

Analysis of ADRs by dose in the fixed-dose trials
(Studies 288A, 288AA and 306): No. of Patients (%)

ADR CATEGORY	Daily Dose (by Assignment)	
	200 mg (N=193)	300 mg (N=196)
X. <u>SKIN AND APPENDAGES</u>		
PRURITUS	1 (0.5%)	2 (1.0%)
RASH	3 (1.6%)	2 (1.0%)
XI. <u>SPECIAL SENSES</u>		
VISUAL DISORDERS	2 (1.0%)	3 (1.5%)
TASTE DISORDERS	1 (0.5%)	0
XII. <u>UROGENITAL</u>		
MICTURITION DISORDERS	1 (0.5%)	2 (1.0%)
URINARY TRACT INFLAM.	4 (2.1%)	2 (1.0%)
OTHER GENITAL SYMPTOMS	0	1 (0.5%)
RENAL FUNCTIONAL IMPAIRMENT	3 (1.6%)	3 (1.5%)

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TABLE 6B

Summary of ADRs by dose for ketoprofen-treated patients†
(total N=1638)

ADR CATEGORY	Mean daily dose††			
	unknown	<230 mg	230-270 mg	>270 mg
I. BODY AS A WHOLE				
FEVER/CHILLS	0	3	3	3
LE SYNDROME	0	0	0	1
ALLERGIC REACTIONS	2	10	3	3
PAIN	0	2	0	2
HEADACHE	7	69	12	41
SALICYLISM	0	25	9	22
II. CARDIOVASCULAR				
RHYTHM DISTURBANCES	1	10	1	8
CORONARY ISCHEMIA	0	1	1	2
HYPERTENSION	0	3	3	3
VENOUS DISORDERS	0	0	1	1
CARDIAC INSUFFICIENCY	0	2	1	0
VASODILATION	0	5	0	2
PERIPHERAL ISCHEMIA	0	1	0	0
III. DIGESTIVE				
INCREASED APPETITE	0	3	0	0
ORAL INFLAMMATION	0	12	1	13
OTHER ORAL SYMPTOMS	2	7	0	5
UPPER GI DISTRESS	28	222	48	166
LOWER GI DISTRESS	14	55	16	45
DIARRHEA	9	45	9	42
CONSTIPATION	3	25	9	30
PEPTIC ULCER	4	16	4	12
GI BLEEDING	0	4	1	4
LIVER FUNCTIONAL IMPAIRMENT	1	0	0	2
BILIARY DISORDERS	0	4	1	0

† Excluded from the database:

- Study 189 (blind and open) for concomitant intake of ASA (per protocol)
- Studies 374, 375, 376, 377: single dose
- Studies 122, 135, 158, 169 for inadequate dosage data

†† Mean daily dose was determined by capsule count at each visit (i.e., the number of ketoprofen capsules consumed between two patient visits divided by the number of days between two patients visits). However, when the actual medication consumption record was inadequate (e.g., Study 275B), the prescribed dosage level was used.

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TABLE 6B
(continued)

Summary of ADRs by dose for ketoprofen-treated patients†
(total N=1638)

ADR CATEGORY	Mean daily dose††			
	unknown	<230 mg	230-270 mg	>270 mg
X. SKIN AND APPENDAGES				
PRURITUS	2	11	4	7
SWEATING	0	4	0	2
SEBORRHEA	0	2	1	4
DRY SKIN	0	1	0	2
PIGMENTATION DISORDERS	0	0	0	1
HAIR DISORDERS	0	3	0	3
HEALING DELAYED	0	1	0	0
NAIL DISORDERS	0	1	0	3
SKIN INFECTIONS	0	2	2	4
RASH	2	33	11	25
XI. SPECIAL SENSES				
SMELL DISORDERS	0	0	0	1
PAIN, EAR	0	0	0	2
VISUAL DISORDERS	4	15	6	21
EXTERNAL EYE DISORDERS	2	10	4	4
TASTE DISORDERS	1	4	0	2
XII. UROGENITAL				
MICTURITION DISORDERS	1	12	4	5
URINARY TRACT INFLAMMATION	0	10	3	6
GENITAL BLEEDING	0	4	0	7
OTHER GENITAL SYMPTOMS	0	4	1	1
RENAL FUNCTIONAL IMPAIRMENT	8	33	7	27

TABLE 7

Statistically significant differences in ADR
categories between diagnoses

	RA N=1056	OA N=432	AS N=63	GA N=49	DM N=46	AN N=383
<u>Body as a Whole</u>	OA, GA, AN OA, AN	-	OA, GA, AN	-	-	-
Headache						
Salicylism						
<u>Digestive</u>						
UGI Distress	OA, AN	AN	AN	AN	AN	-
LGI Distress	AN	AN	-	-	-	-
Diarrhea	AN	AN	-	AN	-	-
Constipation	AN	AN	-	-	-	-
Peptic Ulcer	AN	-	-	-	-	-
<u>Metabolic and Nutritional</u>						
Weight Increases	-	-	-	-	-	-
<u>Musculoskeletal</u>						
Myalgia	AN	-	-	-	-	-
<u>Nervous</u>						
Inhibition	OA	-	-	-	RA, OA, AS GA, AN	OA
Excitation/Nerv.	OA	-	-	-	-	-
<u>Respiratory</u>						
Upper Respiratory Inflammation	OA, AN	-	-	-	-	-

RA = rheumatoid arthritis, OA = osteoarthritis, AS = ankylosing spondylitis, UGI = upper gastrointestinal
GA = gouty arthritis, DM = dysmenorrhea, AN = analgesic

The diagnoses listed in the columns were associated with a significantly lower incidence of ADRs
as compared to the diagnoses shown in the column headings.

TABLE 7
(Continued)

Statistically significant differences in ADR
categories between diagnoses

	RA N=1056	OA N=432	AS N=63	GA N=49	DM N=46	AN N=383
<u>Skin</u>						
Pruritus	AN	-	-	-	-	-
Rash	OA, AN	AN	-	-	-	-
<u>Special Senses</u>						
Visual Disorders	AN	-	-	-	-	-
Ext. Eye Disorders	AN	-	-	-	-	-
<u>Urogenital</u>						
Micturition Disorders	AN	-	-	-	-	-
Renal Funct. Impairment	AN	AN	-	-	-	-

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TABLE 8

Analysis of ADR by duration of ketoprofen treatment†: No. of Patients (%)

ADR CATEGORY	Duration††	
	≤ 30 days N=1545	> 30 days N=1355
I. <u>BODY AS A WHOLE</u>		
FEVER/CHILLS	1 (0.1%)	7 (0.5%)
LE SYNDROME	0	1 (0.1%)
ALLERGIC REACTIONS	7 (0.5%)	11 (0.7%)
PAIN	2 (0.1%)	2 (0.1%)
HEADACHE	83 (5.4%)	51 (3.8%)
SALICYLISM	14 (0.9%)	42 (3.1%)
II. <u>CARDIOVASCULAR</u>		
RHYTHM DISTURBANCES	7 (0.5%)	14 (1.0%)
CORONARY ISCHEMIA	1 (0.1%)	3 (0.2%)
HYPERTENSION	2 (0.1%)	7 (0.5%)
VENOUS DISORDERS	0	2 (0.1%)
CARDIAC INSUFFICIENCY	0	3 (0.2%)
VASODILATION	2 (0.1%)	4 (0.3%)
PERIPHERAL ISCHEMIA	0	1 (0.1%)
III. <u>DIGESTIVE</u>		
INCREASED APPETITE	1 (0.1%)	2 (0.1%)
ORAL INFLAMMATION	6 (0.4%)	20 (1.5%)
OTHER ORAL SYMPTOMS	7 (0.5%)	7 (0.5%)
UPPER GI DISTRESS	219 (14.2%)	238 (17.6%)
LOWER GI DISTRESS	39 (2.5%)	91 (6.7%)
DIARRHEA	41 (2.6%)	58 (4.3%)
CONSTIPATION	22 (1.4%)	44 (3.3%)
PEPTIC ULCER	2 (0.1%)	34 (2.5%)

† The following studies are included (total number of patients = 1545)

- a) RA= 201, 210, 306 (blind and open), 142, 158, 182, 226, 268, 270 (blind only), 243 (open only), 350 (open only)
- b) OA= 275, 288, 289, 288AA (blind and open) 135, 169 (blind only)
- c) AS= 297-I and 297-II (blind only)

Excluded are 1-week or shorter studies and Study 189 (incl. 189A).

†† Duration categories are not mutually exclusive (i.e., the 1355 patients of the >30 days sample are included in the the total of 1545 enrolled patients).

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TABLE 8
(continued)

Analysis of ADR by duration of ketoprofen treatment: No. of Patients (%)

ADR CATEGORY	Duration	
	≤ 30 days N=1545	> 30 days N=1355
III. <u>DIGESTIVE</u> (Cont'd)		
GI BLEEDING	1 (0.1%)	7 (0.5%)
LIVER FUNCTIONAL IMPAIRMENT	0	3 (0.2%)
BILIARY DISORDERS	0	5 (0.4%)
IV. <u>ENDOCRINE</u>		
THYROID DISORDERS	0	1 (0.1%)
V. <u>HEMIC AND LYMPHATIC</u>		
LEUKOPENIA	0	1 (0.1%)
ANEMIA	2 (0.1%)	7 (0.5%)
COAGULATION DISORDERS	2 (0.1%)	10 (0.7%)
VI. <u>METABOLIC AND NUTRITIONAL</u>		
WEIGHT DECREASE	0	3 (0.2%)
WEIGHT INCREASE	5 (0.3%)	4 (0.3%)
THIRST	2 (0.1%)	1 (0.1%)
VII. <u>MUSCULOSKELETAL</u>		
PAIN, BACK	2 (0.1%)	6 (0.4%)
MYALGIA	3 (0.2%)	20 (1.5%)
VIII. <u>NERVOUS</u>		
NEUROMUSCULAR DISORDERS	1 (0.1%)	2 (0.1%)
PSYCHOTIC DISORDERS	1 (0.1%)	0
TACTILE DISORDERS	4 (0.3%)	5 (0.4%)
INHIBITION	44 (3.0%)	87 (6.4%)
EXCITATION/NERVOUSNESS	22 (1.4%)	24 (1.8%)
BALANCE DISORDERS	2 (0.1%)	5 (0.4%)
IX. <u>RESPIRATORY</u>		
RESPIRATORY BLEEDING	0	4 (0.3%)
UPPER RESPIRATORY INFLAMMATION	8 (0.5%)	19 (1.4%)

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TABLE 8
(continued)

Analysis of ADR by duration of ketoprofen treatment: No. of Patients (%)

ADR CATEGORY	Duration	
	≤ 30 days N=1545	> 30 days N=1355
IX. <u>RESPIRATORY</u> (Cont'd)		
BRONCHOPULMONARY DISORDERS	4 (0.3%)	5 (0.4%)
X. <u>SKIN AND APPENDAGES</u>		
PRURITUS	10 (0.6%)	14 (1.0%)
SWEATING	1 (0.1%)	5 (0.4%)
SEBORRHEA	2 (0.1%)	5 (0.4%)
DRY SKIN	0	3 (0.2%)
PIGMENTATION DISORDERS	0	1 (0.1%)
HAIR DISORDERS	0	6 (0.4%)
HEALING DELAYED	0	1 (0.1%)
NAIL DISORDERS	0	4 (0.3%)
SKIN INFECTIONS	1 (0.1%)	7 (0.5%)
RASH	15 (1.0%)	58 (4.3%)
XI. <u>SPECIAL SENSES</u>		
SMELL DISORDERS	0	1 (0.1%)
PAIN, EAR	0	2 (0.1%)
VISUAL DISORDERS	13 (0.8%)	33 (2.4%)
EXTERNAL EYE DISORDERS	7 (0.5%)	14 (1.1%)
TASTE DISORDERS	4 (0.3%)	3 (0.2%)
XII. <u>UROGENITAL</u>		
MICTURITION DISORDERS	11 (0.7%)	12 (0.9%)
URINARY TRACT INFLAMMATION	5 (0.3%)	14 (1.0%)
GENITAL BLEEDING	1 (0.1%)	10 (0.7%)
OTHER GENITAL SYMPTOMS	3 (0.2%)	3 (0.2%)
RENAL FUNCTIONAL IMPAIRMENT	47 (3.0%)	26 (1.9%)

TABLE 9

Analysis of ADRs by concomitant medication: No. of Patients (%)

ADR CATEGORY	All Concomitant Medication Except Gold and Corticosteroids					
	None N=315	Diuretic N=239	Beta- Blocker N=53	Anti- allergy N=30	Insulin or Oral Antidiabetics N=16	Thyroid Supplements N=59
I. BODY AS A WHOLE						
FLUVER/CHILLS	0	1 (0.4%)	1 (1.9%)	0	0	0
LE SYNDROME	0	0	0	0	0	2 (0.5%)
ALLERGIC REACTIONS	5 (1.6%)	1 (0.4%)	0	0	0	0
PAIN	0	1 (0.4%)	0	0	0	3 (0.8%)
HEADACHE	17 (5.4%)	7 (2.9%)	3 (5.7%)	2 (4.0%)	0	0
SALICYLISM	3 (1.0%)	3 (1.3%)	0	0	1 (6.3%)	15 (4.1%)
						5 (1.4%)
II. CARDIOVASCULAR						
RHYTHM						
DISTURBANCES	5 (1.6%)	2 (0.8%)	0	0	0	5 (1.4%)
CORONARY ISCHEMIA	0	0	1 (1.9%)	0	0	2 (0.5%)
HYPERTENSION	0	0	1 (1.9%)	0	0	0
VENOUS DISORDERS	0	0	0	1 (2.0%)	0	0
CARDIAC						
INSUFFICIENCY	1 (0.3%)	1 (0.4%)	1 (1.9%)	0	0	0

† Only the studies listed below are included, since concomitant medication data were not collected for other studies.

(a) RA = 306 (blind and open)

(b) OA = 215 (open only), 288, 289, 288AA (blind and open) (c) AS = 297-I and 297-II (blind only)

(d) GA = 298 (open only), 354 (blind only) (e) PS = 299 (open only)

Note:

The concomitant drug classes listed above (from diuretic to "other") are not mutually exclusive (e.g., a patient could have received diuretic and beta-blocker). Analysis for each concomitant drug class vs. "none" (i.e., ketoprofen only) was performed (χ^2 test for 2x2 table).

* $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ (vs. "none")

TABLE 9
(continued)

Analysis of ADRs by concomitant medication: No. of Patients (%)

ADR CATEGORY	All Concomitant Medication except Gold and Corticosteroids							"Other" Drugs N=305
	None N=315	Diuretic N=239	Beta- Blocker N=75	Anti- diabetic N=30	Insulin or Oral Antidiabetics N=15	Thyroid Supplements N=55		
II. CARDIOVASCULAR (cont'd)								
VASODILATION	0	1 (0.4%)	1 (1.3%)	0	0	1 (1.7%)	1 (0.3%)	0
PERIPHERAL ISCHEMIA	0	0	0	0	0	0	0	0
III. DIGESTIVE								
INCREASED APPETITE	1 (0.3%)	0	0	0	0	0	0	0
ORAL INFLAMMATION	4 (1.3%)	1 (0.4%)	0	0	0	2 (3.4%)	5 (1.4%)	0
OTHER ORAL SYMPTOMS	1 (0.3%)	4 (1.7%)	0	1 (2.0%)	0	1 (1.7%)	3 (0.8%)	0
UPPER GI DISTRESS	79 (25.1%)	67 (28.3%)	21 (39.6%)*	10 (20.0%)	7 (43.8%)	23 (40.0%)*	100 (27.5%)	0
LOWER GI DISTRESS	20 (6.3%)	23 (9.7%)	4	5 (10.0%)	0	9 (15.3%)*	33 (9.1%)	0
DIARRHEA	22 (7.0%)	14 (5.9%)	3 (5.7%)	2 (4.0%)	0	3 (5.1%)	25 (6.9%)	0
CONSTIPATION	5 (1.6%)	6 (2.5%)	0	3 (6.0%)	2 (12.5%)	2 (3.4%)	25 (6.9%)*	0
PEPTIC ULCER	10 (3.2%)	6 (2.5%)	0	0	0	1 (1.7%)	7 (1.9%)	0
GI BLEEDING	2 (0.6%)	0	0	0	0	0	2 (0.5%)	0
LIVER FUNCTIONAL IMPAIRMENT	2 (0.6%)	0	0	0	0	0	0	0
BILIARY DISORDERS	0	0	0	0	0	0	1 (0.3%)	0
IV. ENDOCRINE								
THYROID DISORDERS	0	0	0	0	0	1 (1.7%)	0	0

* p<0.05, ** p<0.01, *** p<0.001 (vs "none")

TABLE 9
(continued)

Analysis of ADRs by concomitant medication: No. of Patients (%)

ADR CATEGORY	All Concomitant Medication Except Gold and Corticosteroids					
	None N=315	Diuretic N=239	Beta- blocker N=53	Anti- allergy N=50	Insulin or Oral Antidiabetics N=16	Thyroid Supplements N=59
V. HEMIC AND LYMPHATIC						
L (UKOPENIA	1 (0.3%)	0	0	0	0	0
ANEMIA	4 (1.3%)	0	0	0	0	0
COAGULATION						
DISORDERS	3 (1.0%)	0	0	0	0	1 (0.3%)
VI. METABOLIC AND NUTRITIONAL						
WEIGHT DECREASE	1 (0.3%)	1 (0.4%)	0	0	0	0
WEIGHT INCREASE	1 (0.3%)	4 (1.7%)	0	0	0	1 (0.3%)
THIRST	2 (0.6%)	1 (0.4%)	0	0	0	4 (1.3%)
VII. MUSCULOSKELETAL						
PAIN, BACK	2 (0.6%)	0	1 (1.9%)	0	0	0
MYALGIA	2 (0.6%)	1 (0.4%)	0	0	0	0
VIII. NERVOUS						
PSYCHOTIC DISORDERS	0	0	0	0	0	0
NEUROMUSCULAR						
DISORDERS	0	0	0	0	0	1 (0.3%)
TACTILE DISORDERS	1 (0.3%)	0	0	1 (2.0%)	0	0
INHIBITION	11 (3.5%)	0	0	0	0	1 (0.3%)
EXCITATION/						
NERVOUSNESS	5 (1.6%)	6 (2.5%)	2 (3.8%)	2 (4.0%)	1 (6.3%)	9 (15.3%)**
						29 (8.0%)
						12 (3.3%)

* p ≤ 0.05, ** p ≤ 0.01 (vs. "none")

TABLE 9
(continued)

Analysis of ADRs by concomitant medication: No. of Patients (%)

ADR CATEGORY	All Concomitant Medication Except Gold and Corticosteroids					
	None N=315	Diuretic N=239	Beta- blocker N=51	Anti- allergy N=50	Insulin or Oral Antidiabetics N=16	Thyroid Supplements N=59
VIII. NERVOUS (Cont'd)						
BALANCE DISORDERS	1 (0.3%)	0	0	1 (2.0%)	0	1 (1.7%)
IX. RESPIRATORY						
RESPIRATORY BLEEDING	1 (0.3%)	1 (0.4%)	0	0	0	0
UPPER RESPIRATORY INFLAMMATION	2 (0.6%)	4 (1.7%)	0	0	0	0
BRONCHOPULMONARY DISORDERS	0	2 (0.8%)	0	0	1 (6.3%)	3 (0.8%)
X. SKIN AND APPENDAGES						
PRURITUS	2 (0.6%)	5 (2.1%)	1 (1.9%)	0	0	6 (1.6%)
SWEATING	0	0	0	0	0	1 (0.3%)
SEBORRHEA	1 (0.3%)	1 (0.4%)	0	0	0	0
DRY SKIN	0	0	0	0	0	0
PIGMENTATION DISORDERS	0	0	0	0	0	0
HAIR DISORDERS	1 (0.3%)	0	0	0	0	0
HEALING DELAYED	0	0	0	0	0	0
NAIL DISORDERS	1 (0.3%)	1 (0.4%)	0	0	0	1 (0.3%)
SKIN INFECTIONS	0	0	0	0	0	1 (0.3%)
RASH	8 (2.5%)	10 (4.2%)	0	4 (8.0%)	0	21 (5.8%)

TABLE 9
(continued)
Analysis of ADRs by concomitant medication: No. of Patients (%)

ADR CATEGORY	All Concomitant Medication Except Gold and Corticosteroids					
	None N=315	Diuretic N=239	Beta- blocker N=53	Anti- allergy N=50	Insulin or Oral Antidiabetics N=16	Thyroid Supplements N=59
XI. SPECIAL SENSES						
SMELL DISORDERS	0	0	0	0	0	0
PAIN, EAR	0	1 (0.4%)	0	0	0	0
VISUAL DISORDERS	6 (1.9%)	4 (1.7%)	0	1 (2.0%)	0	0
EXTERNAL EYE DISORDERS	0	0	0	1 (2.0%)	0	0
TASTE DISORDERS	1 (0.3%)	1 (0.4%)	0	0	0	1 (1.7%)
XII. UROGENITAL						
MICTURITION DISORDERS	2 (0.6%)	1 (0.4%)	0	0	0	1 (1.7%)
URINARY TRACT INFLAMMATION	4 (1.2%)	3 (1.3%)	2 (3.8%)	0	0	0
GENITAL BLEEDING	0	1 (0.4%)	0	0	0	1 (1.7%)
OTHER GENITAL SYMPTOMS	0	1 (0.4%)	0	1 (2.0%)	0	0
RENAL FUNCTIONAL IMPAIRMENT	9 (2.9%)	19 (7.9%)*	6 (11.3%)*	2 (4.0%)	0	6 (10.2%)*
						17 (4.7%)

* p < 0.05 (vs. "none")

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TABLE 10

Analysis of ADRs by age group
(short-term studies excluded†): No. of Patients (%)

ADR CATEGORY	Age Group		
	< 45 years N=323	45-60 years N=623	> 60 years N=599
I. BODY AS A WHOLE			
FEVER/CHILLS	1 (0.3%)	6 (1.0%)	1 (0.2%)
LE SYNDROME	0	1 (0.2%)	0
ALLERGIC REACTIONS	5 (1.7%)	6 (1.0%)	7 (1.2%)
PAIN	1 (0.3%)	2 (0.3%)	1 (0.2%)
HEADACHE	49 (15.2%)	50 (8.0%)	35 (5.8%)
SALICYLISM	12 (3.7%)	25 (4.1%)	19 (3.2%)
II. CARDIOVASCULAR			
RHYTHM DISTURBANCES	3 (1.0%)	8 (1.1%)	10 (1.7%)
CORONARY ISCHEMIA	0	4 (0.5%)	0
HYPERTENSION	4 (1.4%)	3 (0.5%)	2 (0.3%)
VENOUS DISORDERS	1 (0.3%)	1 (0.2%)	0
CARDIAC INSUFFICIENCY	0	0	3 (0.5%)
VASODILATION	0	3 (0.5%)	3 (0.5%)
PERIPHERAL ISCHEMIA	0	1 (0.2%)	0
III. DIGESTIVE			
INCREASED APPETITE	0	2 (0.3%)	1 (0.1%)
ORAL INFLAMMATION	5 (1.7%)	13 (2.1%)	8 (1.3%)
OTHER ORAL SYMPTOMS	1 (0.3%)	4 (0.6%)	9 (1.5%)
UPPER GI DISTRESS	98 (30.3%)	184 (29.5%)	175 (29.2%)
LOWER GI DISTRESS	17 (5.8%)	56 (9.0%)	57 (9.5%)
DIARRHEA	26 (8.0%)	43 (6.9%)	30 (5.0%)
CONSTIPATION	11 (3.4%)	27 (4.3%)	28 (4.7%)
PEPTIC ULCER	2 (0.7%)	15 (2.4%)	19 (3.2%)

† The following studies are included (total number of patients = 1545)

(a) RA = 201, 210, 306 (blind and open), 142, 158, 182, 226,

268, 270 (blind only), 243 (open only); 350 (open only)

(b) OA = 275 (open only), 288, 289, 288AA (blind and open), 135, 169
(blind only).

(c) AS = 297-I and 297-II (blind only)

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TABLE 10
(continued)

Analysis of ADRs by age group
(short-term studies excluded): No. of Patients (%)

ADR CATEGORY	Age Group		
	< 45 years N=323	45-60 years N=623	> 60 years N=599
III. <u>DIGESTIVE</u> (Cont'd)			
GI BLEEDING	0	4 (0.6%)	4 (0.7%)
LIVER FUNCTIONAL IMPAIRMENT	1 (0.3%)	2 (0.3%)	0
BILIARY DISORDERS	1 (0.3%)	1 (0.2%)	3 (0.5%)
IV. <u>ENDOCRINE</u>			
THYROID DISORDERS	0	1 (0.2%)	0
V. <u>HEMIC AND LYMPHATIC</u>			
LEUKOPENIA	1 (0.3%)	0	0
ANEMIA	3 (1.0%)	3 (0.5%)	3 (0.5%)
COAGULATION DISORDERS	2 (0.7%)	8 (1.3%)	2 (0.3%)
VI. <u>METABOLIC AND NUTRITIONAL</u>			
WEIGHT DECREASE	0	2 (1.3%)	1 (0.2%)
WEIGHT INCREASE	2 (0.7%)	5 (0.8%)	2 (0.2%)
THIRST	1 (0.3%)	2 (0.3%)	0
VII. <u>MUSCULOSKELETAL</u>			
PAIN, BACK	1 (0.3%)	4 (0.6%)	3 (0.5%)
MYALGIA	4 (1.0%)	10 (1.6%)	9 (1.5%)
VIII. <u>NERVOUS</u>			
PSYCHOTIC DISORDERS	0	0	1 (0.2%)
NEUROMUSCULAR DISORDERS	0	1 (0.2%)	2 (0.3%)
TACTILE DISORDERS	3 (1.0%)	4 (0.6%)	2 (0.3%)
INHIBITION	35 (10.8%)	56 (9.0%)	40 (6.7%)
EXCITATION/NERVOUSNESS	12 (4.1%)	19 (3.1%)	15 (2.5%)
BALANCE DISORDERS	1 (0.3%)	3 (0.5%)	3 (0.5%)
IX. <u>RESPIRATORY</u>			
RESPIRATORY BLEEDING	1 (0.3%)	3 (0.5%)	0
UPPER RESPIRATORY INFLAMMATION	8 (2.5%)	13 (2.1%)	6 (1.0%)

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TABLE 10
(continued)Analysis of ADRs by age group
(short-term studies excluded): No. of Patients (%)

ADR CATEGORY	Age Group		
	< 45 years N=323	45-60 years N=623	> 60 years N=599
IX. <u>RESPIRATORY</u> (Cont'd)			
BRONCHOPULMONARY DISORDERS	3 (0.9%)	1 (0.2%)	5 (0.8%)
X. <u>SKIN AND APPENDAGES</u>			
PRURITUS	4 (1.2%)	11 (1.8%)	9 (1.5%)
SWEATING	1 (0.3%)	3 (0.5%)	2 (0.3%)
SEBORRHEA	1 (0.3%)	2 (0.3%)	4 (0.7%)
DRY SKIN	0	3 (0.5%)	0
PIGMENTATION DISORDERS	1 (0.3%)	0	0
HAIR DISORDERS	1 (0.3%)	3 (0.5%)	2 (0.3%)
HEALING DELAYED	0	1 (0.2%)	0
NAIL DISORDERS	0	3 (0.5%)	1 (0.2%)
SKIN INFECTIONS	1 (0.3%)	2 (0.3%)	5 (0.8%)
RASH	11 (3.4%)	35 (5.6%)	27 (4.5%)
XI. <u>SPECIAL SENSES</u>			
SMELL DISORDERS	0	1 (0.2%)	0
PAIN, EAR	1 (0.3%)	1 (0.2%)	0
VISUAL DISORDERS	7 (2.2%)	17 (2.7%)	22 (3.7%)
EXTERNAL EYE DISORDERS	5 (1.5%)	12 (1.9%)	4 (0.7%)
TASTE DISORDERS	1 (0.3%)	1 (0.1%)	5 (0.8%)
XII. <u>UROGENITAL</u>			
MICTURITION DISORDERS	4 (1.2%)	10 (1.6%)	9 (1.5%)
URINARY TRACT INFLAMMATION	3 (1.0%)	7 (1.1%)	9 (1.5%)
GENITAL BLEEDING	6 (1.9%)	4 (0.6%)	1 (0.2%)
OTHER GENITAL SYMPTOMS	2 (0.6%)	3 (0.5%)	1 (0.2%)
RENAL FUNCTIONAL IMPAIRMENT	8 (2.7%)	26 (4.2%)	39 (6.5%)

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TABLE 11
Analysis of ADRs by sex
(short-term studies excluded†): No. of Patients (%)

ADR CATEGORY	Male N=482	Female N=1063	Total N=1545
I. <u>BODY AS A WHOLE</u>			
FEVER/CHILLS	3 (0.6%)	5 (0.5%)	8 (0.6%)
LE SYNDROME	0	1 (<0.1%)	1 (<0.1%)
ALLERGIC REACTIONS	4 (0.8%)	14 (1.3%)	18 (1.2%)
PAIN	0	4 (0.4%)	4 (0.3%)
HEADACHE	28 (5.8%)	** 106 (10.0%)	134 (8.7%)
SALICYLISM	20 (4.1%)	36 (3.4%)	56 (3.6%)
II. <u>CARDIOVASCULAR</u>			
RHYTHM DISTURBANCES	2 (0.4%)	19 (1.8%)	21 (1.4%)
CORONARY ISCHEMIA	1 (0.2%)	3 (0.3%)	4 (0.3%)
HYPERTENSION	4 (0.9%)	5 (0.5%)	9 (0.6%)
VENOUS DISORDERS	1 (0.2%)	1 (<0.1%)	2 (0.1%)
CARDIAC INSUFFICIENCY	1 (0.2%)	2 (0.2%)	3 (0.2%)
VASODILATION	0	6 (0.6%)	6 (0.4%)
PERIPHERAL ISCHEMIA	1 (0.2%)	0	1 (<0.1%)
III. <u>DIGESTIVE</u>			
INCREASED APPETITE	1 (0.2%)	2 (0.2%)	3 (0.2%)
ORAL INFLAMMATION	5 (1.0%)	21 (2.0%)	26 (1.7%)
OTHER ORAL SYMPTOMS	4 (0.8%)	10 (1.0%)	14 (0.9%)
UPPER GI DISTRESS	113 (23.4%)	*** 344 (32.4%)	457 (29.6%)
LOWER GI DISTRESS	41 (8.5%)	89 (8.4%)	130 (8.4%)
DIARRHEA	21 (4.4%)	* 78 (7.3%)	99 (6.4%)
CONSTIPATION	13 (2.7%)	53 (5.0%)	66 (4.3%)
PEPTIC ULCER	11 (2.3%)	25 (2.4%)	36 (2.3%)

† The following studies are included (total number of patients = 1545)

* p<0.05
** p<0.01
*** p<0.001

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TABLE 11
(continued)

Analysis of ADRs by sex
(short-term studies excluded): No. of Patients (%)

ADR CATEGORY	Male N=482	Female N=1063	Total N=1545
III. <u>DIGESTIVE</u> (Cont'd)			
GI BLEEDING	1 (0.2%)	7 (0.7%)	8 (0.5%)
LIVER FUNCTIONAL IMPAIRMENT	1 (0.2%)	2 (0.2%)	3 (0.2%)
BILIARY DISORDERS	0	5 (0.5%)	5 (0.3%)
IV. <u>ENDOCRINE</u>			
THYROID DISORDERS	0	1 (<0.1%)	1 (<0.1%)
V. <u>HEMIC AND LYMPHATIC</u>			
LEUKOPENIA	0	1 (<0.1%)	1 (<0.1%)
ANEMIA	1 (0.2%)	8 (0.8%)	9 (0.6%)
COAGULATION DISORDERS	4 (0.8%)	9 (0.8%)	12 (0.8%)
VI. <u>METABOLIC AND NUTRITIONAL</u>			
WEIGHT DECREASE	1 (0.2%)	2 (0.2%)	3 (0.2%)
WEIGHT INCREASE	1 (0.2%)	8 (0.8%)	9 (0.6%)
THIRST	1 (0.2%)	2 (0.2%)	3 (0.2%)
VII. <u>MUSCULOSKELETAL</u>			
PAIN, BACK	4 (0.8%)	4 (0.4%)	8 (0.5%)
MYALGIA	4 (0.8%)	19 (1.8%)	23 (1.5%)
VIII. <u>NERVOUS</u>			
PSYCHOTIC DISORDERS	0	1 (<0.1%)	1 (<0.1%)
NEUROMUSCULAR DISORDERS	0	3 (0.3%)	3 (0.2%)
TACTILE DISORDERS	3 (0.6%)	6 (0.6%)	9 (0.6%)
INHIBITION	25 (5.2%)	** 106 (10.0%)	131 (8.5%)
EXCITATION/NERVOUSNESS	9 (1.9%)	37 (3.5%)	46 (3.0%)
BALANCE DISORDERS	1 (0.2%)	6 (0.6%)	7 (0.5%)
IX. <u>RESPIRATORY</u>			
RESPIRATORY BLEEDING	1 (0.2%)	3 (0.3%)	4 (0.3%)
UPPER RESPIRATORY INFLAMMATION	5 (1.0%)	22 (2.1%)	27 (1.7%)
BRONCHOPULMONARY DISORDERS	3 (0.6%)	6 (0.6%)	9 (0.6%)

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TABLE 11
(continued)

Analysis of ADRs by sex
(short-term studies excluded): No. of Patients (%)

ADR CATEGORY	Male N=482	Female N=1063	Total N=1545
X. SKIN AND APPENDAGES			
PRURITUS	6 (1.3%)	18 (1.7%)	24 (1.5%)
SWEATING	4 (0.8%)	2 (0.2%)	6 (0.4%)
SEBORRHEA	4 (0.8%)	3 (0.3%)	7 (0.5%)
DRY SKIN	1 (0.2%)	2 (0.2%)	3 (0.2%)
PIGMENTATION DISORDERS	0	1 (<0.1%)	1 (<0.1%)
HAIR DISORDERS	0	6 (0.6%)	6 (0.4%)
HEALING DELAYED	1 (0.2%)	0	1 (<0.1%)
NAIL DISORDERS	0	4 (0.4%)	4 (0.3%)
SKIN INFECTIONS	4 (0.8%)	4 (0.4%)	8 (0.5%)
RASH	21 (4.4%)	52 (4.9%)	73 (4.7%)
XI. SPECIAL SENSES			
SMELL DISORDERS	0	1 (<0.1%)	1 (<0.1%)
PAIN, EAR	1 (0.2%)	1 (<0.1%)	2 (0.1%)
VISUAL DISORDERS	14 (2.9%)	32 (3.0%)	46 (3.0%)
EXTERNAL EYE DISORDERS	6 (1.3%)	15 (1.4%)	21 (1.4%)
TASTE DISORDERS	3 (0.6%)	4 (0.4%)	7 (0.5%)
XII. UROGENITAL			
MICTURITION DISORDERS	3 (0.6%)	20 (1.9%)	23 (1.5%)
URINARY TRACT INFLAMMATION	5 (1.0%)	14 (1.3%)	19 (1.2%)
GENITAL BLEEDING	0	11 (1.0%)	11 (0.7%)
OTHER GENITAL SYMPTOMS	2 (0.2%)	4 (0.4%)	6 (0.4%)
RENAL FUNCTIONAL IMPAIRMENT	18 (3.8%)	55 (5.2%)	73 (4.7%)

TABLE 12

Distribution of ADR from Published Reports on Ketoprofen Treatment in 10,824 Patients

Total side effect reports - 2305

Gastrointestinal	CNS/Sensory	General	Skin	Cardiovascular	Genitourinary	Musculoskeletal	Respiratory
abdominal pain 569	dizziness/vertigo 92	unspecified 137	local suppuratory intolerance 137	palpitation 92	polyuria 7	muscle aches/3 cramps	epistaxis 1
GI intolerance 257	headache 60	fever 9	rash, maculopapular and nonpapular 48	chest pain 5	dysuria 3		nasal congestion 1
vomiting 225	mood changes 34	malaise/fatigue 15	pruritus 15	hypertension 5	frequency of micturition 1		
dyspepsia 164	somnolence 30	perspiration 9	injection site reaction 9	flushing 3			
nausea 133	insomnia 9	fever 8	hives 8				
constipation 73	taste disturbance 8	weight gain 3	bruises 3				
gastric distress 66	eye disorders 6	thirst 2	dryness 2				
diarrhea 63	hearing disorders 4	elevated BUN 1	hair loss 1				
flatulence 24	abnormal dreams 4						
anorexia 18	asthenia 2						
peptic ulcer 16	paresthesia 1						
oral cavity symptoms 14	hypesthesia 1						

(Continued on the next page)

Onidis®: Summary Basis of Approval

-101-

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TABLE 12 (Cont'd)

Distribution of ADR from Published Reports on Ketoprofen Treatment in 10,823 Patients

Total side effect reports - 2305

Gastrointestinal	CNS/Sensory	General	Skin	Cardiovascular	Genitourinary	Musculoskeletal	Respiratory
hematemesis/ melena	11 forgetfulness	1					
fecal occult blood	7 difficulty concentrating	1					
rectal pain	4						
ulcerative colitis	1						
Total: 1645 (% of 2305): (71%)	262 (11%)	191 (8%)	167 (7%)	22 (1%)	11 (.5%)	5 (.2%)	2 (.1%)

*Distribution of side effects among the organ systems by numbers and percent of total side effects.

N-18754-3

NDA

18-754

Approval

Letters



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

NDA 18-754

JAN 9 1986

Ives Laboratories
685 Third Avenue
New York, New York 10017

Attention: Robert H. Harris, Ph.D.
Director, Regulatory Affairs

Dear Dr. Harris:

Reference is made to your new drug application dated March 15, 1982 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orudis (ketoprofen) Capsules 50 and 75 mg.

We also acknowledge receipt of your additional communications dated November 21, 1983 and December 3, 1984 and to your letter of December 13, 1985 in which you made a commitment to perform a Phase IV carcinogenicity study in rats. We also note the following additional Phase IV commitments:

1. To perform additional pharmacokinetic studies in a sufficient number of elderly and renal and hepatic impaired patients to better characterize their mean response as well as their variability (about 24 patients in each category).
2. To obtain and evaluate additional data regarding the patients reported in the British Medical Journal article (291:1609-1610, 1985) by Dr. J. D. O'Brien and Dr. W. R. Burnham as well as usage data for the Romford area.
3. To analyze further the 45 cases of ulcers or bleeding from the 1292 open label ketoprofen patients. This should include a case by case comparison of patients who developed ulcers to those who did not for important risk factors to determine if there is something additional that should be added to the labeling.

We have completed the review of this application including the draft labeling submitted December 27, 1985 and the application is approved, effective on the date of this letter. The following changes must be made in the labeling:

CLINICAL PHARMACOLOGY (eighth and ninth paragraphs)

To date, studies of the effects of age and renal function impairment have been small, generally involving 5-8 subjects per group, but they indicate modest decrease in clearance in the elderly and in patients with impaired renal function. In normal elderly volunteers (mean age 73 years), the plasma and renal clearance and protein binding were reduced while the V_d increased when compared to a younger normal population (mean age 27 years). (Plasma clearance and V_d were 0.05 l/kg/hr and 0.4 l/kg/hr in elderly and 0.06 l/kg/hr and 0.3 l/kg/hr in young subjects, respectively.) The mean half-life of ORUDIS in this normal geriatric population as well as in a rheumatoid elderly population (mean age 64 years) was about 5 hours as compared to 3 hours in the younger population.

Patients with impaired renal function (mean age 44 years) also demonstrate decreases in plasma clearance (0.04 l/kg/hr) of drug, with the mean half-life increasing to about 3.5 hours.

Carcinogenesis, Mutagenesis, Impairment of Fertility

(Insert after first sentence) A chronic oral toxicity study was also performed in rats (up to 12.5 mg/kg/day) with no statistically significant increase in any tumor type; however, this study was unacceptable because of poor survival.

WARNINGS

Replace "approximately 1% per year" with "greater than 1% per year (see ADVERSE REACTIONS)".

ADVERSE REACTIONS

Insert as the second sentence in the second paragraph the following:

Peptic ulcer or G.I. bleeding occurred in controlled clinical trials in less than 1% of 1076 patients; however, in open label continuation studies in 1292 patients the rate was greater than 2%. The incidence of peptic ulceration in patients on NSAIDs is dependent on many risk factors including age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticoids, as well as the dose and duration of treatment with NSAIDs (see WARNINGS).

ADVERSE REACTIONS (continued)

Under Incidence greater than 1%, an asterisk should be added after "CNS inhibition (i.e., pooled reports of somnolence, malaise, depression, etc.) or excitation (i.e., insomnia, nervousness, dreams, etc.)" and after "Impairment of renal function (edema, increased BUN)".

DOSAGE AND ADMINISTRATION (first paragraph)

The recommended daily dose of ORUDIS is 150-300 mg, divided in three or four doses. The recommended starting dose is 75 mg three times or 50 mg four times a day. If minor side effects appear, they may disappear at a lower dose which may still have an adequate therapeutic effect. If well tolerated but not optimally effective, the dosage may be increased. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well controlled clinical trials patients on 300 mg did not show greater mean effectiveness. They did, however, show an increased frequency of upper and lower G.I. distress and headaches. It is of interest that women also had an increased frequency of these adverse effects compared to men. When treating patients with 300 mg a day, the physician should observe sufficient increased clinical benefit to offset potential increased risk. Dosages higher than 300 mg per day are not recommended because they have not been adequately studied. Relatively small people may need smaller doses.

The labeling should be revised exactly as we have requested and twelve copies of the final printed version of the revised labeling must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA renders the product misbranded under 21 U.S.C. 352.

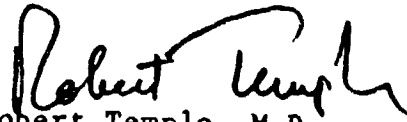
Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revisions of that labeling may be required.

Page 4
NDA 18-754

Please submit one market package of the drug products when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Robert Temple". The signature is fluid and cursive, with the first name "Robert" and last name "Temple" clearly distinguishable.

Robert Temple, M.D.

Director

Office of Drug Research and Review
Center for Drugs and Biologics

Supp.

Letters



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

18-754/S001

JAN 27 1986

Ives Laboratories
685 Third Avenue
New York, New York 10017

Attention: Robert H. Harris, Ph.D.
Director, Regulatory Affairs

Dear Dr. Harris:

Please refer to your supplemental new drug application dated January 14, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orudis (ketoprofen) Capsules.

This supplement provides for final printed labeling incorporating the revisions requested in our approval letter of January 9, 1986 and the draft labeling submitted December 27, 1985.

We have completed our review of this supplement and it is approved. We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-754/S-003, S-004

Wyeth Laboratories Inc.
P.O. Box 8299
Philadelphia, Pennsylvania 19101

Attention: Micheal J. Krieg
Director, Regulatory Affairs

Dear Mr. Krieg:

Reference is made to your supplemental new drug applications dated April 21, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orudis (ketoprofen) Capsules.

We also refer to our approvable letter of January 20, 1987 and to your additional communications of March 2 (final printed labeling), May 19 (Phase IV commitments), June 9 (response to a telephone request from our Division of Biopharmaceutics) and July 16, 1987 (Phase IV dose proportionality commitment).

These supplemental applications provide for additional indications in mild to moderate pain and dysmenorrhea, for the addition of a 25 mg capsule and for revision of the Drug Interactions section of the labeling to add interactions with methotrexate and lithium.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on March 2, 1987. Accordingly, the supplemental applications are approved, effective on the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Page 2

cc:

Orig. NDA 18-754/S-003, S-004

HFN-150/Div.File

HFN-83

HFN-730

HFN-232

HFN-240

HFN-100

HFN-150/DWPease 7-10-87

HFN-150/ESheinin

R/D Init. by:RScully 7-17-87

DJRichman 7/13/87

RHuckins 7-10-87

ESheinin 7-10-87

DWPease 7-10-87

JGHarter 7-15-87

F/T:Mickey 7-20-87

Wang# 10680

RScully
7/27/87

20

Wyeth Laboratories Inc.
P.O. Box 8299
Philadelphia, Pennsylvania 19101-8299

Attention: Joseph N. Bathish
Director
Regulatory Affairs

Dear Mr. Bathish:

Please refer to your supplemental new drug applications dated April 21, 1986 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Orudis (ketoprofen) Capsules.

These supplemental applications provide for the additional indications of mild to moderate pain and dysmenorrhea and for two additions to the Drug Interactions section regarding methotrexate and lithium.

We have completed our review of these supplemental applications and they are approvable. Before these supplemental applications may be approved, however, we request that you submit the following:

1. We note that you have proposed a dosage of 50 mg q.i.d. for dysmenorrhea. This dose has not been studied directly; however, because of the results of the three dysmenorrhea studies, we agree that, based on these studies, this is the proper dose to recommend. We also note that you have studied loading doses; however, those studies did not establish that they should be recommended. Therefore, we request that you commit to performing Phase IV studies in dysmenorrhea comparing 25 and 50 mg q.i.d. to higher doses q.i.d. and investigating more rigorously the effects of loading doses.
2. Please submit 12 copies of final printed labeling that are identical to the draft copy submitted April 21, 1986 with the following revisions:
 - a. In the Clinical Pharmacology section, add "The effectiveness of Orudis as a general purpose analgesic has been studied in standard pain models which have shown the effectiveness of doses of 25 - 150 mg. Doses of 25 mg were superior to placebo. Larger doses than 25 mg generally could not be shown significantly

more effective but there was a tendency toward faster onset and greater duration of action with 50 mg and, in the case of dysmenorrhea, a significantly greater effect overall with 75 mg. Doses greater than 50 - 75 mg did not have increased analgesic effect".

- b. In the Warnings section, the statement reading "... new peptic ulcers keep appearing in patients under treatment with ketoprofen at a rate of greater than 12 per year..." should be changed to read "... new peptic ulcers keep appearing in patients under treatment with ketoprofen at a rate of greater than 20 per year...".
- c. In the Precautions section, under "Carcinogenesis, Mutagenesis, Impairment of Fertility", the following should be added: "Abnormal spermatogenesis or inhibition of spermatogenesis developed in rats and dogs at high doses, and a decrease in the weight of the testes occurred in dogs and baboons at high doses". This request is based on the studies submitted on the original NDA and was inadvertently not included in our January 9, 1986 approval letter.
- d. In the Adverse Reactions section, "Causal Relationship Unknown" should be in parentheses and should have the heading "Incidence Less than 1%".
- e. In the Dosage and Administration section, headings for indications should be added, i.e., "Rheumatoid Arthritis and Osteoarthritis: The recommended dose...". In addition, the Mild to Moderate Pain and Dysmenorrhea section should be changed to read "The usual dose of Orudis recommended for mild to moderate pain and dysmenorrhea is 25 - 50 mg every 6-8 hours as necessary. A smaller dose should be utilized initially in small individuals, in debilitated or elderly patients or in patients with renal or liver disease (see PRECAUTIONS). A larger dose may be tried if the patient's response to a previous dose was less than satisfactory, but doses above 75 mg have not been shown to give added analgesia. Daily doses above 300 mg are not recommended because they have not been adequately studied. Because of its typical nonsteroidal anti-inflammatory drug side effect profile, including as its principle adverse effect GI side effects (see WARNINGS and ADVERSE REACTIONS), higher doses of Orudis should be used with caution and patients receiving them observed carefully".

The labeling should be revised exactly as we have requested and 12 copies of the final printed version of the revised labeling must be submitted to FDA. Marketing of the drug for these indications ~~by~~ ^{once} the changes specified above are made and submitted to FDA as the products misbranded under 21 U.S.C. 352. Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

The warnings section revision above may be modified subsequent to our review of the following additionally-requested information:

1. In order that we may evaluate your hypothesis that the increased ulcer rate in studies 288AA/OL and 305L is due to the higher doses used, please submit, for each patient from any study or open label follow up who developed an ulcer or had upper GI bleeding, a summary table and figure that relates time on ketoprofen to dose of ketoprofen, concomitant therapy and occurrence of all ADR signs or symptoms. As supporting documents, please submit the case report forms, all supporting letters, memos, and hospital records for all of the peptic ulcer patients.
2. Please submit a listing of the doses administered to those patients who developed ulcers at the time they developed their ulcers.
3. We do not agree with the exclusion of the eight patients for questionable ulcers. Please recalculate and redo the life tables excluding only patients DRB 2011A Pt No 2 and DRB 243 Pt No 1 (U.I.).
4. You should develop denominators for all dosage levels based on the highest dose which patients received for at least 1 month (i.e., patients should be counted only one time). The denominators should be divided into RA, OA and "other". It should be possible to audit the denominators to find for each patient, the studies in which they were involved and the doses of ketoprofen that they received.
5. Please prepare and submit a "audit trail" or "balance sheet" which permits one to see where each of the patients referenced in Enclosure 9 (a) of the March 15, 1980 submission originated study by study, patient by patient.

Page 4

NDA 18-754/S-003, S-004

Finally, because we are recommending a starting dose of 25 mg, it will be necessary for you to amend this supplement (S-003) to add this dosage strength. This amendment should refer to the original NDA for data on the 25 mg strength and should provide assurance that the manufacturing/controls are exactly the same as in the original submission. These data have already been reviewed by our chemist and we are expediting the biopharmaceutics review for the 25 mg strength. Any additional stability data on the 25 mg strength should also be submitted at this time.

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Oncology and Radiopharmaceutical Drug Product, HFN-150, and the Division of Drug Advertising and Labeling, HFN-240, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the above absence of such action, FDA may take action, to withdraw the supplemental applications.

The drug may not be legally marketed for these indications before you have been notified in writing that these supplemental applications are approved.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Chem

15121
Dr. J. B. F. Laboratories,
6557 Third Avenue,
New York, N.Y. 10017

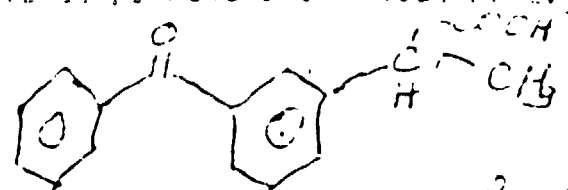
Received: 10-10-85
Date: 10/13/85
Pearce

Product Name(s): *Cardis
Metoprolol*

FINISHED REVIEW
Date: 10/14/85

Patent Number: FL-19589, 19583 R.P.

Drug Name(s) and Dose(s) of Administration: *Cardis 25mg, 50mg,
100mg*
Therapeutic Category and/or Principal Indication: *Anti-hypertensive*
Chemical Name & Chemical Structure: *2-(S)-benzoylphenyl-propionic acid*



Initial Submission: *March 15, 1982*
Amendment(s): *December 3, 1984*
Related Documents: [REDACTED]

Remarks:

*all questions have been satisfactorily answered by
J.B.F. therefore as they have withdrawn their
at first flexible wrap package (see memo) -
then their application is approvable in regard
to chemical controls. (Bivariate labelity data
is being evaluated by Division of Pharm-
aceuticals.*

Conclusions and Recommendations: *The application is approvable
in regard to chemical controls.*

Robert N. Huchkins
Chemist

CC: IND/DA C-10
FDA-100/REGISTRATION
FDA-100/DIV FILE
FDA-100/CSO
Dated by: R.N. Huchkins
Chemist 10-4-85

Handwritten: 9/23/85

Handwritten: 10/13/85

Handwritten: 10/14/85

SEP 10 1984

DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS

NDA#: 18-754

Division: HFN-150

Applicant/Sponsor: Ives Laboratories, Inc.
685 Third Avenue
New York, N.Y. 10017

Chemist Review: ~~45~~ 3
Date Completed: 7/17/84

Product Names:

Proprietary: Orudis
Non-Proprietary: Ketoprofen
USAN: Oxaprozin
Code Name: IL-19589; 19583RP

Dosage Form(s) and Route of Administration:

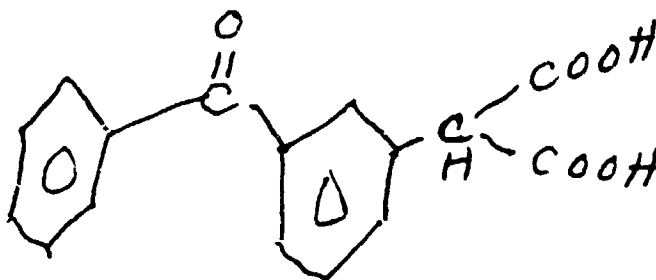
oral, capsules, containing 25 mg, 50 mg, 75 mg, and 100 mg

Pharmacological Category and/or Principal Indication:

Anti-inflammatory agent

Structural Formula and Chemical Name:

2 (3-benzoylphenyl)-propionic acid



- B. 1. Initial Submission: March 15, 1982
2. Amendment(s): August 24, 1983 (Description of capsule shells)
December 29, 1983

Remarks:

The NDA is still non-approvable in respect to chemical controls until the following information is submitted:

1. The level of impurities present in all lots that have been used in the clinical, stability, and bioavailability studies.
2. The write up of the TLC procedure should specify the use of anhydrous ~~solvent~~ in the preparation of the developing solvent.

3. The writeup of the [REDACTED] method should show that the mobile phase is deoassed by filtration and also that the sample solution are either filtered or centrifuged before analysis.
4. The thickness of the HDPE containers should be submitted.
5. Submit the size of the HDPE containers used in the testing of the HDPE containers for capsules according to USP XX. Also, identity the HDPE resin used in the fabrication of each container that was tested.

Conclusions and Recommendations:

Submission is still non-approvable- see draft.

Robert N. Huckins
Robert N. Huckins

cc:
Orig NDA 18-754
HFN-150/Div File
HFN-150/Pease/Behrens ✓
R/D Init by: RHwood/7-17-84
F/T: Dj/7-19-84
Wang #3136P

R.A. Janni
8/18/84

MAR 7 - 1984

Division of Oncology and Radiopharmaceutical Drug Products

Chemist Review #2

Date Completed: 12/1/83

NDA 18-754

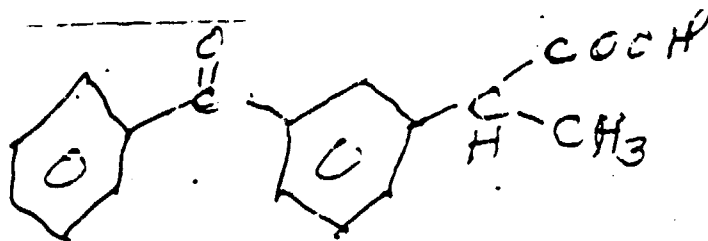
Applicant: Ives Laboratories
685 Third Avenue
New York, New York 10017

Product Name(s): Proprietary: Orudis
Non proprietary: ketoprofen
Code name/number: IL-19589; 19583RP

Dosage Form(s) and Route(s) of Administration: oral, capsules 25, 50, 75 and 100 mg (only 50 and 100 mg will be marketed).

Pharmacological Category and/or Principal Indication: anti-inflammatory agent.

Structural Formula & Chemical Name: 2(3-benzoylphenyl)-propionic acid



Initial Submission: March 15, 1982

Amendments: June 28, 1983 (BD date 6/28/83 received by me July 1, 1983).

Remarks: Memo from HFN-420 has these comments about the validation of methods by DDC Lab and Phila/DO Lab:

1. Methods are suitable for regulatory and control purposes, once the following minor deficiencies are corrected.
 - (1) The preparation of the developing solvent for [redacted] system II requires use of [redacted]. It is necessary to specify whether the anhydrous or hydrate form is to be used, or to specify the molar concentration of the solution.
 - (2) The [redacted] method does not specify filtration of the mobile phase, or filtration of the standard and sample solutions. The solutions should be filtered to protect the column and injection systems.

Page 2
NDA 18-754

Not adequate response to following questions:

1. All USP XX tests for HDPE containers for capsules have not been performed.
2. Letter of authorization from manufacturer of capsules body for information/composition.
3. Physical dimensions for HDPE containers should be submitted.
4. Need initial values for dissolution study but don't have them.

Conclusions and Recommendations: Issue a non-approvable letter - see draft.

Robert N. Huckins
Robert N. Huckins

cc: Orig NDA 18-754
HFN-150/Div File
HFN-150
HFN-150/Huckins
(HFN-150/Pease)
R/D endorsed by: RHWood/12/7/83
F/t by P. Amoss/12/ /83
Wang #0854

RHWood
1/26/84

R. A. Janni
2/17/84

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA# 18754

APPLICANT Ives Laboratories Inc.
SPONSOR: 6857 Third Avenue Avenue
ADDRESS: New York, N.Y. 10017

DIVISION NAME: HFN-150

CHEMIST REVIEW #1

REVIEWING CHEMIST: Robert Huckins

DATE COMPLETED: 9/24/82

PRODUCT NAME(s):

Proprietary: Orudis

Non-proprietary: ketoprofen

Compendium:

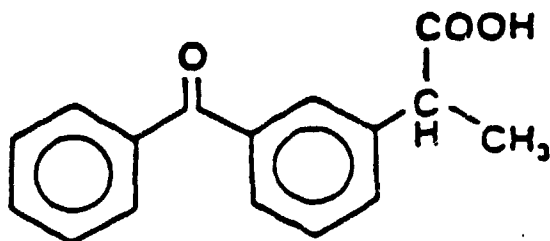
USAN:

Code name/number: IL-19589; 19583 R.P.

DOSAGE FORM(s) AND ROUTE(s) of ADMINISTRATION: Oral, capsule 25 mg, 50 mg 75 mg and 100 mg (50 mg and 100 mg caps are to be marketed)

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Anti-inflammatory

STRUCTURAL FORMULA & CHEMICAL NAME: 2(3-benzoylphenyl)-propionic acid



INITIAL SUBMISSION: March 15, 1982

(Received 8/12/82)

AMENDMENT(s): June 16, 1982

RELATED DOCUMENTS: [REDACTED]

REMARKS: Samples have been sent to the New York District Lab and O.P.R.T. Lab for validation of methods. An inspection has been requested for [REDACTED] manufacture of new drug substance. A letter outlining deficiencies have been sent to Ives Laboratories Inc. holder of NDA and [REDACTED]. The specifications and tests on the HDPE and glass bottles are not satisfactory.

CONCLUSIONS AND RECOMMENDATIONS: Not approvable - see draft of chemist's portion of NDA letter.

Robert N. Huckins
ROBERT N. HUCKINS
CHEMIST

cc: IND/NDA Orig
HFN-150

HFN-180, HFN-102

HFN-150/DOCUMENTS

HFN-150/RHuckins

R/D Endorsed by: RHWood 10/8/82

F/T: cgm: 10/20/82

Ra Jew
12/2/82

109,121
PA
5-18-87

CHEMIST'S REVIEW (If necessary, continue any item on 8" x 10 1/2" paper. Key continuation to item by number.)		1. ORGANIZATION HFN-150	2. NDA NUMBER 18-754
3. NAME AND ADDRESS OF APPLICANT (City and State) Wayth Laboratories Philadelphia, PA 19101		4. AF NUMBER	5. SUPPLEMENT (S) NUMBER(S) DATE(S) 5003 4-21-86
6. NAME OF DRUG Orudex	7. NONPROPRIETARY NAME ketoprofen	9. AMENDMENTS AND OTHER (Reports, etc) DATES SNC 3/2/87	
8. SUPPLEMENT(S) PROVIDES FOR: nequality the 25mg strength tablet		12. RELATED IND/NDA/DMF(S)	
10. PHARMACOLOGICAL CATEGORY Anti-inflammatory agent	11. HOW DISPENSED ☒ RX ☐ OTC	16. RECORDS AND REPORTS CURRENT ☐ YES ☐ NO REVIEWED ☐ YES ☐ NO	
13. DOSAGE FORM (S) capsules	14. POTENCY (mg) 25 mg	15. CHEMICAL NAME AND STRUCTURE	
17. COMMENTS The finished final review of 10/4/85 recommends approval of the 25mg, 50mg, 75mg and 100mg. All necessary control information has been submitted at the request of medical reviewer the 25mg capsule was not included in approval letter as the indication was not approved. Amendment of 3/2/87 provided for expansion of current stability commitment to cover the 25mg capsules control information is still satisfactory.			
18. CONCLUSIONS AND RECOMMENDATIONS ~~Issue an approval letter~~ The 25mg capsule strength is approvable as far as controls are concerned.			
19. REVIEWER NAME: Robert N. Harkins DATE COMPLETED: 4/30/87			
DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE			

Pharm

Pharmacology and Toxicology Review of
NDA 18-754

NOV 4 1983

ADDENDUM TO AMENDMENT OF 9/9/82

SPONSOR: Ives Laboratories, Inc.

SUBMISSION: Amendment of 9/9/82

DRUG: Orudis (Ketoprofen)

SUMMARY AND EVALUATION:

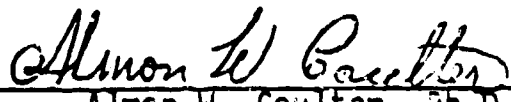
A request was sent to the Division of Biometrics (HFN-715) on 11/17/82 for a statistical evaluation of the 91 week rat carcinogenicity study. Of concern was the occurrence of pituitary adenomas in both sexes and of mammary adenomas in the female.

The summary data which was enclosed with the request did not afford an investigation of exact time of death, therefore the survival history of each treatment group was abstracted from volumes 1.68, 1.69, and 1.70 for the analysis. The method described in "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments" by R. Peto, et al., Annex of IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans, Supp. 2, 1980, WHO Publications, was used to test for a significant positive trend in carcinogenicity with respect to dose. A copy of the statistical review dated March 7, 1983 is attached.

The results of the statistical analysis showed a positive trend of increasing pituitary adenomas with increasing doses in both male and female rats and of mammary adenomas in female rats.

These statistical conclusions were discussed with Ives in a meeting with the firm on April 12, 1983. We agreed to do a different statistical analysis of these tumors and the firm would reevaluate their data by the Peto method.

No further action is needed at this time. We will review the firms statistical analysis of the rat carcinogenicity study and make a decision at that time.


Almon W. Coulter, Ph.D.

cc: Orig NDA 18-754
HFN-150

HFN-150/Div File

HFN-150/Coulter

HFN-150/Moore/Podliska

R/D endorsed by: DJR/ichman/10/11/83

F/T by P. Amoss/10/23/83

Wang #050CP

1

157

PHARMACOLOGY AND TOXICOLOGY REVIEW OF
NDA 18-754

NOV 3- 1982

AMENDMENT OF 9/9/82

DATE REVIEW COMPLETED: 9/30/82

SPONSOR: Ives Laboratories Inc.
New York, N.Y. 10017

SUBMISSION: NDA original amendment dated September 9, 1982. Received in HFN-150 on September 10, 1982 and received by reviewer on September 20, 1982

DRUG: Orudis (Ketoprofen)

CATEGORY: Anti-inflammatory

PATIENT MEMOS/CORRESPONDENCE: This amendment contains answers to the questions communicated to Ives by D. Moore (CSO) on August 30, 1982. Answers to the six questions are indicated below.

QUESTION 1: A list addressing all points has been appended (Attachment I)

QUESTION 2: The presence of a testicular tubular adenoma indeed existed in animal #186. This was a rare hermaphroditic baboon which had gonadal tissue resembling both ovaries and testes, but which externally resembled a female rather than a male baboon. An adenoma derived from testicular tissue was presented in one of the organs.

QUESTION 3: None of the female rats of the high-dose treatment group had an adenocarcinoma of the pancreas. This was a transposition error which occurred in Table 3.7 of Vol 1.1

QUESTION 4: The heading for each group should read rats instead of rabbits. The headings were mislabelled.

QUESTION 5: The two missing pages have been provided in attachment II.

QUESTION 6: Values for the oral LD50 in rabbits and dogs were obtained from the literature and the articles are provided in attachment III.

SUMMARY AND EVALUATION: From the additional data requested from the rat carcinogenicity study (question 1), it appears that Ketoprofen increased the number of pituitary tumors in the treated animals (Table 1). However, there is no dose response relationship in the data.

TABLE 1
NUMBER OF PITUITARY ADENOMAS FOUND IN RATS

	Week 89	92	104
Control	10 (25)*	12 (30)	30 (62)
Low Dose	30 (50)	31 (51)	45 (72)
Mid dose**	18 (34)	23 (39)	
High dose**	18 (36)		

*The numbers in parenthesis include the animals which died on test and/or were sacrificed in moribund condition.

** Dosing period (91 weeks) were followed by a 13 week observation period. High dose males were killed after 89 weeks of treatment. Mid dose males were killed after one week in observation period.

This study was a marginal carcinogenicity study at best (21 months). Because of the high mortality, the surviving males treated at 7 mg/kg/day were killed after 89 weeks of treatment and males in the mid group (4.5 mg/kg/day) were killed after 93 weeks. The surviving controls, low dose males (3 mg/kg/day) and females from all groups were killed at week 104, following a 13 week observation period.

It is difficult to determine if there is any significance in the numbers given in Table 1. The data should therefore be evaluated by our statisticians.

RECOMMENDATIONS: It is recommended that the data on pituitary adenomas in the rat carcinogenicity study be evaluated by our statisticians.


A. W. COULTER, Ph.D

CC
ORIG NDA 18-754
(HFN-150)
HFN-150, HFN-180
HFN-150/AWCOULTER: 9/30/82
HFN-150/CSO/DMoore
R/D ENDORSED BY: DJRichman: 10/8/82
F/T:rgp:10/18/82

wjg
11/1/82

PHARMACOLOGY AND TOXICOLOGY REVIEW OF
NDA 18-754

MAR 9 - 1984

Amendment of July 7, 1983

SPONSOR: Ives Labs. Inc.
New York, N.Y. 10017

Review Completed: 2/29/84

SUBMISSION: Amendment dated July 7, 1983. Received in HFN-150 on July 8, 1983. Received by reviewer on 7/14/83.

DRUG: Orudis (Ketoprofen) or 19583RP

PERTINENT MEMOS/CORRESPONDENCE:

This amendment contains the following documents in response to our meeting with Ives on April 12, 1983 concerning the 91 week rat carcinogenicity study:

- 1) Analysis of Pathology.
- 2) Further statistical analysis of pituitary and mammary gland tumor data.
- 3) Review of sections of pituitary glands.
- 4) Statistical analysis of revised pituitary tumor data.
- 5) Review of mammary and pituitary tumor data for long term rat carcinogenicity study on ketoprofen conducted at Huntingdon Research Centre.
- 6) Concurrent historical control data for two year carcinogenicity studies with Sprague - Dawley rats - comments and summary tabulation.
- 7) Curriculum vitae - F.J.C. Roe, M.D.

DISCUSSION:

The firm's re-evaluation of the 91 week rat study was done by Dr. Francis Rowe, a consultant pathologist with excellent qualifications. The statistical analysis was re-evaluated by Mr. Peter Lee, a consultant statistician and one of the authors of the Peto paper, also well qualified to evaluate these data by this statistical method.

In the submitted document, the points are made by P. N. Lee that our statistical analysis looked at the tumors as if all were a cause of mortality, and that we used a one tailed test. These points will be addressed by the Division of Biometrics. Mr. Lee also makes the statement

"...results are presented of the incidence of malignant mammary tumors as this is strictly the only test of carcinogenicity." The PMA Guidelines state that "A carcinogenic response in long term animal studies consists of a positive finding in either sex of one or both of the following two criteria: a) increase in incidence of total tumors, b) increase in incidence of malignant tumors." Furthermore, the WHO report - Principles for the Testing and Evaluation of Drugs for Carcinogenicity, WHO tech. Rep. Ser., 1969, No. 426 - states that the tumors seen may be benign or malignant.

In Lee's analysis, only at the low dose (3 mg/K) were malignant tumors found at a somewhat higher incidence than occurred in the controls (p = 0.1). No dose related trend was seen. His conclusion was that 19583RP did not significantly affect the incidence of mammary gland tumors or of pituitary tumors in females. The results are indicated in the following tables.

Mammary Gland Tumor Data - Females

		<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>Overall</u>	<u>Trend</u>
Benign or Malignant tumor (visible)	p* =	---	N.S**	N.S	N.S	N.S	N.S
Benign or Malignant tumor (fatal)	p =	---	N.S	N.S	N.S	N.S	N.S
Benign or Malignant tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Malignant tumor (fatal)	p =	---	< 0.1	N.S	N.S	N.S	N.S
Malignant tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S

Pituitary Hyperplasia/Tumor Data - Males

		<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>Overall</u>	<u>Trend</u>
Hyperplasia or Tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Hyperplasia (incidental) or Tumor (fatal)	p =	---	< 0.1	< 0.05	N.S	N.S	N.S
Tumor (incidental)	p =	---	< 0.1	N.S	N.S	N.S	N.S
Tumor (fatal)	p =	---	< 0.01	< 0.01	< 0.05	< 0.05	< 0.05

Pituitary Hyperplasia/Tumor Data - Females

		<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>Overall</u>	<u>Trend</u>
Hyperplasia or Tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Hyperplasia (incidental) or Tumor (fatal)	p =	---	< 0.1	N.S	N.S	< 0.1	N.S
Tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Tumor (fatal)	p =	---	N.S	N.S	N.S	N.S	N.S

Pituitary Hyperplasia/Tumor Data - Male and Female

		<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>	<u>Overall</u>	<u>Trend</u>
Hyperplasia or Tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Hyperplasia (incidental) or Tumor (fatal)	p =	---	< 0.01	N.S	< 0.1	< 0.1	< 0.1
Tumor (incidental)	p =	---	N.S	N.S	N.S	N.S	N.S
Tumor (fatal)	p =	---	< 0.01	< 0.05	< 0.05	< 0.05	< 0.01

*p = significance

**N.S. = not significant

We note that Lee's results agree with our analysis, i.e., that a significant trend ($p < 0.05$) was observed in the number of pituitary adenomas in male rats. Lee states that the apparent effect could be an artifact of misclassification of incidental tumors as fatal and suggested that further analysis be done on males after an attempt is made to classify individual pituitary tumors as fatal or incidental, based on malignancy, size, or other relevant consideration.

The rat pituitary sections were then examined by Dr. Roe, who reclassified the tumors as:

- 1) Pituitary tumors likely to have caused death or contributed to the cause of death.
- 2) Pituitary tumors unlikely to have caused or have contributed to the cause of death.

The following notes are as follows:

Key H = hyperplasia
 T = tumour
 O = other hyperplasia or tumour

	Sex	Animal No.	ERC	FJCR
	M	12	O	H
		42	O	T
	M	65	H	T
		66	T	H
		67	O	T
		72	O	H
		80	O	T
		88	O	H
		102	O	H
		112	Invaded by Neurofibroma	Primary Craniopharyngioma
3	M	170	O	H
		178	O	H
4	M	181	O	H
		190	O	H
		229	O	T
1	F	243	T	H
		248	H	T
		253	O	H
		255	O	H
		258	O	T
		260	O	H
		274	O	H
		279	O	H
		285	O	T
		286	O	H
		290	O	H
		293	O	T (see para. 4 below)
		294	O	T
		298	O	T
2	F	350	T	H
		353	O	H
		355	H	O
		357	O	H
3	F	361	O	H
		362	O	T
		364	O	H
		366	O	H
		377	O	H
		382	O	H
		387	O	H
		402	O	T
		404	O	T
		411	T	H
4	F	424	O	H
		425	O	H

There were 48 differences between Dr. Gopinath's (Huntingdon Research Center's pathologist) and Dr. Roe's microscopic findings. Dr. Roe suggested that alternate statistical analysis be carried out on the following assumptions.

- 1) That malignant tumors are fatal and benign tumors and hyperplasia are not fatal.
- 2) That malignant tumors and benign tumors of more than 6 mm diameter (macroscopically) are fatal and that all smaller benign tumors and hyperplasia are not fatal.

The 48 differences are indicated in the table on page 4.

A second statistical analysis was done by Mr. Lee using the reevaluated data. The pituitary hyperplasia/tumor data for males, females, and combined sexes were presented for the following:

- 1) Malignant tumors only.
- 2) Benign or malignant tumors - assuming large benign tumors incidental.
- 3) Benign or malignant tumors - assuming large benign tumor fatal.
- 4) Tumors or hyperplasia - assuming large benign tumors incidental.
- 5) Tumors or hyperplasia - assuming large benign tumors fatal.

A rat was classified as having a large benign tumor if either macroscopic or microscopic measurements exceeded 6 mm. Lee's analysis is given below along with the results from his first analysis.

Pituitary Hyperplasia/Tumor Data - Pinales

First Analysis Tumor (fatal)		Control	Low	Mid	High	Overall	Trend
0	21	21	28	20	15		
χ^2	33.14	21.77	14.81	14.29	5.41	9.82	6.29
P		< 0.01	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05
Second Analysis Benign or malignant (assuming large benign tumors fatal)		Control	Low	Mid	High	Overall	Trend
0	22	22	30	20	16		
χ^2	29.18	22.50	18.49	17.82	2.71	6.06	0.91
P		< 0.05	N.S	< 0.1	N.S	N.S	N.S

Lee now observed no trend in male pituitary tumors (benign and malignant, assuming large benign tumors as fatal). A significant increase was observed only in the low ($p < 0.05$) and high ($p < 0.1$) dose among these tumors. There was also a significant ($p < 0.05$) negative trend observed in females with malignant tumors.

Mr. Lee concludes "...there is little evidence that 19583RP might have an adverse effect on pituitary tumor incidence." He attributes the relatively weak level of significance in the low and high groups to a chance variation, rather than a carcinogenic effect.

The current historical control data from seven two year carcinogenicity studies with Sprague-Dawley rats at Huntingdon Research Center were included in this submission and are summarized in table form below.

Historical Control For Pituitary and Mammary Adenomas

Historical Controls	Pituitary Adenomas		Mammary Adenomas
	Males	Female	Female
Mean	35.9% (+ 8.5)	55.7% (+ 16.4)	22.1% (+ 12.1)
Range	25% - 47%	36% - 84%	7% - 40%
Ketoprofen Control	37%	38%	13%
3.0 mg/kg	49%	43%	21%
4.5 mg/kg	37%	30%	23%
7.0 mg/kg	27%	35%	15%

The historical control data were derived from 104 week studies started between February 1973 and April 1974. It is therefore current with the ketoprofen study (June 1975 to March 1977). It is not known if all controls were evaluated by the same pathologist. The data indicated that at the low dose the incidence of pituitary adenomas in males was slightly higher than the high range of the historical controls and that the high dose female group was slightly below the low range of the historical controls. These values are not strictly comparable due to the high death rate in the mid and high dose groups; the high death rate reduces the exposure time, which in turn, reduces the incidence of these tumors. Nevertheless, the incidence of pituitary adenomas in the ketoprofen control was slightly higher than found in the historic male mean control.

If one looks at the survival time in this study (see below), it is noted that 50% of the high dose males were dead at week 76; at week 89, which is the time the high dose group was terminated, the survival rate was only 17%. The mid dose males were killed at week 92

Fifty Percent Survival Time (Weeks)		
Dose (mg/kg)	Male	Female
0	96	96
3.0	84	88
4.5	80	92
7.0	76	84

with 17% survivors. It must also be remembered that ketoprofen was administered for only 91 weeks and not 104 weeks.

Ives amendment was reviewed by the Division of Biometrics, HFN-715. The Division's statistical analysis is attached with this review. Their analysis concluded that no significant increase in the number of pituitary tumors exists with increasing doses of ketoprofen. It further states that "significant levels are not reached when using the one or two tailed test, and are not found when using the death rate method or the prevalence method on all pituitary tumors."

In Table 2 of the HFN-715 review, the number of pituitary adenomas in male and female rats used in the statistical reviews is tabulated. It was pointed out that a disproportionate number occurred in appendix IV of the Ives amendment. We should point out that hyperplasias were also included in Table 2 and are not of interest to the discussion of tumors. These numbers point out how difficult it is to do an unbiased retrospective study. (NOTE: Addendum to Ms. Mocaik's review.)

In conclusion, the sponsor has presented revised data which our statisticians find no reason to disagree with. Based on all the data and analysis which have been presented to date, I would conclude that ketoprofen must be considered a weak carcinogen in the Sprague-Dawley rat when tested under the conditions used in this study. It is recommended that the sponsor conduct a two year carcinogenicity study in an alternate strain of rat. The reasons for this recommendation follow:

- a) Although no trend was observed in the revised data presented in Table 1, p62, Appendix IV, the low dose males showed a $p < 0.05$ and the high dose a $p < 0.1$ for pituitary tumors (benign or malignant, assuming large benign tumors fatal).

- b) The incidence of pituitary adenomas in male Sprague-Dawley CD rats in the low dose group of this study was higher (49%) than the upper range (47%) of the historical controls from Huntingdon Research Corporation.
- c) The strain of rat used in this study has a high propensity for developing spontaneous pituitary adenomas.
- d) The high mortality rate which developed in the mid and high dose male groups resulted in terminating the high dose group at week 89 with only 17% survivals and the mid dose group at week 92 with 17% survivals. Only 50% of the high dose group survived to week 76.
- e) The question of accepting Dr. Roe's classification of tumors as fatal or incidental based on size, since (1-) it was done retrospectively and (2-) if the section was not made at the maximum diameter of the tumor, it would appear to be smaller than it may have actually been at autopsy.

RECOMMENDATIONS:

We recommend sponsor conduct a two year carcinogenicity study in a strain of rat which does not have a high background in spontaneous pituitary adenomas.

This submission is not approvable because Ketoprofen has not been adequately tested for carcinogenicity.


Almon W. Coulter, Ph.D.

Addendum: I agree with Dr. Coulter that the rat study should be repeated in another strain for the five reasons he cites. We now have a compound in which the mouse carcinogenicity study was considered negative and the rat study showed limited evidence of activity (one species only, poor survival, high background of spontaneous tumors, not dose related). The final benefit/risk assessment will have to weigh carefully this hint of activity.

cc: Orig NDA 18-754

HFN-150/Div File

HFN-150/Coulter

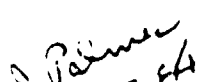
HFN-150/Pease

R/D endorsed by: DJRichman/2/29/84

F/T by P. Amoss/3/5/84

Wang #1559P


David J. Richman, Ph.D.
Supervisory Pharmacologist


3-7-84

PEARL
PHARMACOLOGY AND TOXICOLOGY REVIEW OF
NDA 18-754

AUG 22 1984

Amendment of 4/6/84
Review No. 4

Review Completed: 5/3/84

SPONSOR: Ives Laboratories, Inc.
New York, New York 10017

SUBMISSION: This submission was received by the reviewer on March 3, 1984.

DRUG: Ketoprofen (Orudis)
1L-19,583
19,583 RP

CATEGORY: Anti-inflammatory

MARKETING INDICATION:

This drug is indicated for the long term treatment of the signs and symptoms of musculoskeletal and soft tissue inflammatory conditions including: rheumatoid arthritis, osteoarthritis,

The maintenance dosage for chronic conditions is 100 mg tid or 100-200 mg bid. Dosages above 400 mg/day (8 mg/kg for a 50 kg person) are not recommended.

PERTINENT MEMOS/CORRESPONDENCE:

This submission contains the firm's minutes of the meeting held at FDA on 3/9/84 to discuss the 2 year rat carcinogenicity study.

DISCUSSION:

The Pharm/Tox review of the original submission (3/15/82) was completed on 6/16/82. A statistical evaluation of the two year rat study was requested on 11/17/82. The results of the statistical study showed a (+) trend of increasing pituitary adenomas with increasing doses in both male and female rats. These results were discussed with the firm at a meeting with HFN-150 and HFN-715 (Div. of Biometrics) on 4/12/83. The firm replied to our concerns in amendment of 7/7/83 (See Pharm/Tox Review No. 3).

After reviewing the firm's reevaluation of the pituitary tumor data and the evaluation from the Div. of Biometrics, it was concluded that under

the conditions in which the two year rat study was done, Ketoprofen must be considered a weak tumorigen in the Sprague-Dawley rat. I recommended that the sponsor conduct a two year rat carcinogenicity in an alternate strain of rat. Reasons for this recommendation were:

- a) Although no trend was observed in the revised data, the low dose males showed a $p < 0.05$ and the high dose of $p < 0.1$ for pituitary tumors (benign or malignant, assuming large benign tumors fatal).
- b) The incidence of pituitary adenomas in male Sprague-Dawley CD rats in the low dose group was higher (49%) than the upper range (47%) of the historical controls from Huntingdon Research Corporation.
- c) The strain of rat used in this study has a high propensity for developing spontaneous pituitary adenomas.
- d) The high mortality rate which developed in the mid and high dose male groups resulted in terminating the high dose group at week 89 with only 17% survivals and the mid dose group at week 92 with 17% survivals. Only 50% of the high dose survived to week 76.
- e) The question raised of accepting classification of tumors as fatal or incidental based on size, since (1) it was done retrospectively and (2) if the section was not made at the maximum diameter of the tumor, it would appear to be smaller than it may have actually been at autopsy.

Shortly after the above reasons and recommendation were given to Ives by telecon, the firm requested a meeting. At this meeting (3/9/84) the statistical points were addressed by Mr. , a consultant statistician, and the pathology was discussed by a consultant pathologist.

began by saying he made every effort to avoid bias in re-reviewing the pituitary slides. He said it was essential to make full use of the available microscopic data, and it was therefore not feasible to read the slides blinded.

In regard to point e), said the technician is instructed to ensure that the largest section is prepared from a spherical lesion. Further, the size of a tumor in a section of the pituitary gland is apt to be smaller than the size it appeared to have at necropsy - this is due to shrinkage during processing and also because the knife does not go through the "equator" of a spherical lesion. The problem would apply equally to animals in all groups including the controls and would not have introduced any bias.

Pituitary tumors as a cause of death, according to can theoretically cause death either by obstructing the flow of cerebrospinal fluid causing hydrocephalus, or by effecting the hormones which they produce. In his experience those that cause hydrocephalus are ≥ 10 mm in diameter. Only 5 tumors were this size (2 male control, 1 high dose male, 1 female control, and 1 high dose female), and no cases of hydrocephalus were observed in this bioassay. The point is also made that if pituitary tumors of more than 6 mm diameter had been fatal for any reason, one would expect to find fewer such tumors at the termination of the study.

Regarding the survival of the animals in this study, the results of a comparison for the survival of control rats in the ketoprofen study and in 7 other 2-year carcinogenicity studies conducted at HRC during the same time period are given below.

<u>% Control Survival for Two Year Sprague-Dawley Rats at</u> *			
	<u>Ketoprofen</u>	<u>Mean of 7 Other Studies</u>	<u>Range</u>
Male	27	24	9-56
Female	35	54	38-80

*Charles River CD Sprague-Dawley rats have been used since the mid 70's in carcinogenicity studies at

described his criteria for differentiating hyperplasia, benign neoplasia, and malignant neoplasia as follows:

Hyperplasia: any focus consisting of only one kind of cell.

Benign neoplasia: any expansive lesion with a well demarcated edge and compression of surrounding tissue.

Malignant neoplasia: any lesion exhibiting cellular atypia and/or an increased mitotic rate.

He said many pathologists would not regard these latter criteria as indicative of malignancy and would conclude that no malignant tumors appeared in any animal in this study.

For the statistical analysis it was arranged that use either the macroscopic or the microscopic size of the lesion, whichever was larger. had suggested that benign tumors of more than 6 mm diameter are

fatal, and all smaller benign tumors and hyperplasia are not fatal. Using these assumptions, Lee's statistical analysis is again presented below.

Statistical Analysis of Tumor Data

	<u>3 mg/kg</u>	<u>4.5 mg/kg</u>	<u>7 mg/kg</u>	<u>Overall</u>	<u>Trend</u>
Benign (> 6 mm fatal) and malignant tumors	p < 0.05	N.S	p < 0.1	N.S	N.S
Benign (> 6 mm incidental) and malignant tumors	p < 0.1	N.S	N.S	N.S	N.S
Malignant tumors	N.S	N.S	N.S	N.S	N.S

Our statisticians agree with these values.

It was also argued that most pituitary lesions (hyperplasia or neoplasia in rats are of prolactin producing cells and a relationship exists between high incidence of such pituitary lesions and high incidence of mammary gland hyperplasia, galactorrhoea, and neoplasia. It was stated that overfeeding predisposes the animals to pituitary hyperplasia, prolactinomas, and mammary tumors.

who is now in charge of pathology at , both agree that few if any pituitary tumors in this study were likely to have caused the death of rats. was convinced that the increase in pituitary tumors observed in the low dose males was a chance finding. He said he had never encountered a carcinogenic agent which did not increase the pituitary risk with increase in dosage. It will be recalled that no dose-response relationship was shown in this study.

The poor survival in this study was said not to be due to poor standards of animal care at , the commonest cause of death in the treated and control animals was attributed to chronic progressive glomerulonephritis (44% male, 23% female), with papillary necrosis in the kidney an important lesion (5.3% male, 26% female). Again, it was emphasized that overfeeding greatly influenced chronic progressive nephropathy. It was 's opinion that overfeeding was a more important cause of renal disease and pituitary pathology in rats than genetic make-up. He felt we should have no concern about the strain of rat used or the reduced length of the study.

This reviewer appreciated the opportunity to meet with and . Their additional evidence and arguments were well taken and informative. We are dealing with a rather unusual two year carcinogenicity study; a study which must be considered borderline in its length, statistical outcome, and the way the firm reevaluated the results. It would seem that each in itself would not be a sufficient reason for repeating the study (the statistical result is the most influencing factor), but taken together I would again tend to recommend the sponsor repeat the rat carcinogenicity study in an alternate strain of rat prior to approval of this application.

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NDA 18-754

RECOMMENDATIONS:

We are again recommending that the sponsor repeat the two year carcinogenicity study in a strain of rat which does not have a high background in spontaneous pituitary tumors.

Almon W. Coulter

Almon W. Coulter, Ph.D.

cc: Orig NDA 18-754
HFN-150/Div File
HFN-150/Coulter
HFN-150/Pease/Behrens
R/D endorsed by: DJRichman/5/11/84
F/T by P. Amoss/5/25/84
Wang #2491P

*noted
J Palmer
6-26-84
This needs discussion
in HFN-150 and with
statisticians, too.*

NOV 4 - 1982

Original Summary

Date Review Completed: 6/15/82

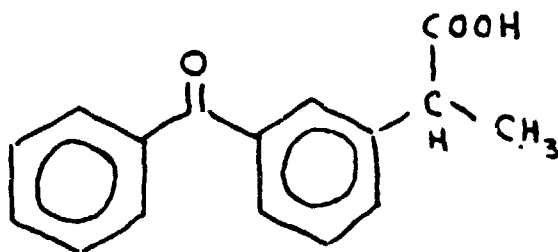
NDA: 18-754

Applicant: Ives Laboratories Incorporated
685 Third Avenue
New York, N.Y. 10017

SUBMISSION: Original submission dated March 15, 1982. Received BD on 3/16/82; received HFD-150 on 3/22/82. Assigned to reviewer c. 3/26/82.

DRUG: Orudis (Ketoprofen)

1L-19,583 or 19,583 R.P.
2(3-Benzoylphenyl)-propionic Acid



CATEGORY: Anti-Inflammatory

PROPOSED MARKETING INDICATION:

Orudis is indicated for the acute or long-term treatment of the signs and symptoms of musculoskeletal and soft tissue inflammatory conditions, including:

1. Rheumatoid arthritis
2. Osteoarthritis
3. Ankylosing spondylitis
4. Acute gouty arthritis
5. Acute painful shoulder syndrome

Orudis is indicated in all acute forms of bursitis, tendinitis, and crystal induced synovitis.

Page 2

the maintenance dosage for chronic conditions is:
100 mg T.I.D. or 100-200 mg B.I.D.

Dosages above 400mg/day are not recommended until further clinical experience is obtained.

RELATED DRUGS/INDs/NDAs:

[REDACTED]

PRECLINICAL STUDIES:

Pharmacology:

- 1) Anti-inflammatory, Analgesic, and Antipruritic Activity
- 2) CNS and GI Effects
- 3) Cardiovascular and Pulmonary Effects
- 4) Effects on Hemostasis
- 5) Diuretic, Choloretic, and Metabolic Effects
- 6) Interaction with Neurochemical Mediators
- 7) Mechanism of Action
- 8) Metabolite Pharmacology

Acute Toxicity - 5 Species
Subacute/Chronic Toxicity

- a) 5 Days in Mice and Rats
- b) 4 Weeks in Rats
- c) 5 Weeks in Rats and Dogs
- d) 6-10 Weeks in Baboons
- e) 3 Months in Rats and Dogs
- f) 12 Months in Baboons
- g) 18 Months in Rats
- h) Carcinogenicity in Mice (18 months) and Rats (21 months).

Reproduction:

Segment I - Rats
Segment II - Rats and Rabbits
Segment III - Mice and Rats

Special Studies:

Mutagenicity
Local Tolerance Tests - Rabbits and Dogs
Immune Function Effects
Toxicity of Intermediates and Impurities

Biopharmaceutics:

Absorption - Rat, Rabbit, Dog, and Monkey
Distribution - Rat
Metabolism - Rat, Rabbit, Dog, Monkey, and Man
Excretion - Rat, Rabbit, Dog, and Monkey

PHARMACOLOGY:

Anti-Inflammatory Activity:

The anti-inflammatory activity of Ketoprofen was determined in the following studies: abscess and edema induced by carrageenan in rats, erythema produced by U.V. in guinea pigs, Selve's granulomatous pouch in rats, granuloma by asbestos implantation in rats, and in experimental arthritis in pigeons. In many of these tests Ketoprofen was comparable to Indomethacin and 10 to 40 times more active than phenylbutazone. Activity was also evident in adrenalectomized rats, indicating that its action was on the tissue and not on the adrenal-pituitary axis.

Analgesic Activity:

Analgesic activity was also comparable to Indomethacin in several tests in mice and rats.

Antipyretic Activity:

The antipyretic effect of Ketoprofen in both the Brewer's yeast-induced hypothermia in rats and the anti-gonococcal vaccine-induced hyperthermia in rabbits was somewhat more active than Indomethacin.

CNS Effects:

Ketoprofen was inactive at 100mg/kg p.o. in several experimental models using mice, rats, and dogs.

GI Effects:

A significant increase in the ulcerogenic index was seen when Ketoprofen was administered orally at 3mg/kg or subcutaneously at 1mg/kg. Lower doses had little if any effect on the GI tract. The drug has a 4-5 times more favorable therapeutic ratio than Indomethacin and 6-8 times more favorable than phenylbutazone.

Effect on Cellular Protein and Nucleic Acid Synthesis:

Ketoprofen had no effect at 10mg/ml on the uptake of ¹⁴-C leu, ¹⁴-C-thymidine, or ³H-uridine in incubated KB cells.

Effect on Immune Function:

No effect was seen in the Jerne plaque assay, or on carbon clearance or tolerance of homologous skin grafts in mice. The host response of mice to grafts was similarly unaffected by Ketoprofen administration (10 mg/kg p.o.)

Cardiovascular and Pulmonary Effects:

Ketoprofen (10 mg/kg, i.v.) had slight effects (hypotension) on the BP of 3 animal species (rabbits, cats, and dogs). At this dosage no significant effect was produced in the frequency or amplitude of respiratory movements of an anesthetized dog.

Effects on Hemostasis:

In vitro tests with ketoprofen greatly inhibited the platelet aggregation induced by collagen or arachidonic acid and was identical in potency to Indomethacin. An iv infusion of ketoprofen (5 µg/kg/min) inhibited the collagen platelet aggregation within 5 minutes in rabbits, and platelet aggregation was still observed at 24 hours with 2mg/kg of ketoprofen. The drug did not alter the coagulation process in dogs treated with warfarin.

Diuretic, Choleretic, and Metabolic Effects:

No diuretic or choleretic effects were produced with 25mg/kg or 50mg/kg p.o., respectively. Serum glucose levels and hepatic glycogen levels of rats were not altered by ketoprofen 15mg/kg p.o.

Interaction with Neurochemical Mediators:

Ketoprofen did not alter the effects of epinephrine, norepinephrine, acetylcholine, histamine, serotonin, or of stimulation on the vagus nerve.

Mechanism of Action:

Prostaglandin (PGE₂ and PGF_{2α}) biosynthesis was inhibited in several tests with ketoprofen; however, indomethacin was somewhat more effective. No change was produced on the thymic weight in young male rats as was observed with steroids (Involution). Ketoprofen treatment stabilizes the rat liver lysosomal membrane in vitro and in vivo. Infectious disease caused by Mycobacterium tuberculosis was not aggravated by ketoprofen. Antibradykinin activity was demonstrated by ketoprofen and naproxen in anesthetized guinea pigs challenged with bradykinin.

Metabolite Pharmacology

Two metabolites of ketoprofen (R.P. 36,356 and R.P. 35,481) showed no significant anti-inflammatory, analgesic, or antiovertic activity at oral doses 15 to 120 times higher than the ED₅₀ doses of ketoprofen.

ACUTE TOXICITY

<u>Species</u>	<u>Sex</u>	<u>Route</u>	<u>LD50 (mg/kg)</u>	
Mouse (1)	MF	p.o.	360	8 day observation
(2)	MF	p.o.	575	
	MF	i.v.	500	
	MF	i.p.	650	
	MF	s.c.	550	
Rat (1)	MF	p.o.	160	10 day observation
(2)	M	p.o.	ca. 56	14 day observation
(2)	F	p.o.	87	14 day observation
(3)	MF	p.o.	475*	
(3)	MF	p.o.	32	
	MF	i.m.	70	
Guinea Pig	?	p.o.	ca. 1300	
		i.v.	ca. 450	
Rabbit	MF	i.m.	ca. 470	15 day observation
Dog	MF	p.o.	> 1000	7 day observation
	MF	i.m.	ca. 600	

*Young rats (52-69g weight range)

Toxic Signs:

Signs which appeared in more than one species included: ataxia, neuromuscular depression, diarrhea, anorexia, weight loss, reduced activity, hypothermia, dark feces, and bradypnea. Other signs which were reported only in the dog include: salivation, somnolence, dark polyuria, tachycardia, staggered gait, and emesis. Mice also showed hyperexcitability and muscular weakness.

SUB-ACUTE/CHRONIC TOXICITY:

MOUSE X5 DAYS:

Following oral administration for 5 days and observation for 8 days after drug administration, the LD₅₀ was 180 mg/kg, which was about 30 X less toxic than Indomethacin.

RAT: X5 DAYS:

A comparative study in rats (5 days treatment + 8 days observation) produced an LD₅₀ = 21 mg/kg. Indomethacin was about 4X more toxic. These animals showed ascites, peritonitis, and ulcerations (often perforated) involving the jejunum and ileum.

RAT: X 5 DAYS: Weanling and Adults

Strain: Charles River (COBS, CD) France

Route: Oral in 10% acacia suspension

Dose Levels: Weanlings: 18, 27, 40, 60, 90, 135mg/kg

Adults: 12, 18, 27, 40, 60, 90 mg/kg

Number: 5/sex/dose

Results

LD₅₀ 170 mg/kg for weanlings

LD₅₀ 13 mg/kg for adults

Microscopic examination revealed fibrinous peritoneal exudates, ulcers in the stomach and small intestine.

RATS: 4 WEEKS:

Strain: Charles River, USA (CD)

Route: Oral, in food

Dose Levels: 0, 6, 12, 25, 50mg/kg

Number: 5/sex/dose level

Results

All high dose animals died and 2/10 of the 25 mg/kg group died. Clinical signs included tympanities, skin pallor, poor coat and lethargy. Peritonitis and fecal occult blood were observed. Fibrous adhesions were found between adjacent sections of the intestinal tract. The small intestine and colon were congested and were often accompanied by hepatic swelling. Peritonitis was given as the cause of death.

RAT: 5 WEEKS:

Strain: Charles River France (COBS, CD)

Route: Oral in 10% gum arabic suspension (5 ml/kg)

Dose Levels: 0, 2, 6, 18, 27, 36mg/kg

Number 5/sex/dose level for 36mg/kg group - 10/sex/dose for others.

Results

Weight gain for the two high dose male groups at week 4 was about 15 to 19% lower than controls. The weight gain for the 6 and 18 mg/kg males was significantly low at week 5. High dose females were significantly low at week 4. Mortality occurred at 18 mg/kg (2/20), 27 mg/kg (2/20), and at 36 mg/kg (5/10). Anemia was observed in the two highest groups and was more severe in the females. The 6mg/kg males had slightly elevated urinary bile salts at termination. Organ weights were not significantly different than controls, however, kidney weights of females in the 2 and 18mg/kg groups were higher than controls. Severe ulcerations and inflammation of the subserosa and submucosa occurred in the small intestine of the two high dose groups. Vascular hyperleukocytosis occurred along with the ulcerations in the liver and was accompanied by parenchymatous changes and peritonitis, also splenic leukocytosis of the red pulp with reticulosis and occasionally proliferation of the large stem cells and megakaryocytes. Renal changes occurred in the 3 high dosed and consisted of conglomerations or a series of dilated cortical and/or medullary tubes. The lumens often contained protein granulations which were rarely PAS positive. One high dose male had a complete regression of the testicles.

Dog: 5 weeks

Strain: Beagle

Route: Oral - one capsule/day

Dose Levels: 0, 2, 6, 18, 36mg/kg/day

Number: 2/sex/dose at 36mg/kg, 1/sex/dose all other groups

Results

No deaths - all high dose and females receiving 18mg/kg had anorexia and were anorexic-high dose also had hemorrhagic diarrhea weight losses up to 20% were noted in several dogs. The dose group developed severe anemia of the regenerative type accompanied by moderate leukocytosis and juvenile erythroblastic hyperplasia of the bone marrow. Dogs in the 18mg/kg group had an increase in the reticulocytes, a decrease in circulating erythrocytes, and slight hyperplasia of the bone marrow. Transient increases in blood urea level in high dose dogs and in bromsulphalein retention in the two high dose groups. These two groups also showed a decrease in serum protein and electrophoretic serum albumin-globulin ratio. Increase in fibrinogen and sedimentation rate in two high or 18mg/kg group, respectively. No significant differences in organ weights was noted. Histological examination revealed gastric ulceration and less severe ulceration in the small intestine of the two high dose animals. Severe hepatic inflammation in high dose dogs, also splenic disorders were observed. Pyelonephritis was observed in high dose dogs. Inhibition of spermatogenesis occurred in the two high dose groups.

Esodon: 6-10 weeks:

Strain: *Papio cynocephalus* or *P. anubis*

Route: Oral, in gelatin capsule

Dose Level: 0, 12, 24 mg/kg/day X 6 weeks

6 for 4 weeks, 48 for 2 weeks, 96 for 2 weeks, and
192/mg/kg/day for 2 weeks for the 10 week group.

Number: 2/sex/dose

Study Site: [REDACTED]

Results

No deaths or clinical signs related to dosing. Weight gain was dose related. The 10 week animals all showed 0 to negative weight gain at weeks 4-6 and 6-10 which resulted in a general loss of body condition. Food consumption was depressed during weeks 8-10. WBCs decreased at week 2 and 4 in the 12 and 24mg/kg group. Hb, RBC, PCV, MCV decreased at week 10 and WBC increased. Urine showed the presence of bile salts. RBCs, and blood pigments at weeks 8-10; fecal occult blood was also reported. Absolute liver, spleen, and pancreas weights were slightly decreased and thymus and thyroid showed a dose-related decrease in the 12 and 24 mg/kg groups. Relative (body wt.) pituitary weight showed a dose related increase and thymus showed a dose related decrease. Uterus, adrenals and female gonads increased in weight. Histopathology reported erosion and ulceration of the gastric mucosa of the stomach, ulceration of the duodenal mucosa, dilation of Brunner's glands, and focal necrosis of renal capilla.

RAT: 3 MONTH:

Strain: Charles River, France (COBS, CD)

Route: Oral, in a 10% aqueous solution of gum arabic, 5ml/kg

Dose Level: 0, 6, 12, 24mg/kg divided into 2 daily doses, except 6mg/kg, administered once daily, 6 days/week

Number: 15/sex/dose

Study Site: [REDACTED]

Results

Low Dose: No deaths, slight decrease in RBCs and hyperleucocytosis with polynuclear elements. Urinary albumin elevated in females. Significant increase in female kidney weight. Ulceration of stomach mucosa, hematopoiesis in the splenic red pulp.

Mid Dose: Four deaths (weeks 5, 7, 9, 11), one accidental. Weight loss (2%) with progressive pallor and ascites. Decrease in RBCs, slight hyperleucocytosis with polynucleosis. Elevated male AP and serum BSP value. Urinary albumin elevated in females. Significant increase in male heart weight. Small ulcerations of the stomach mucosa, splenic hypertrophy with hematopoietic activity in the red pulp.

High Dose: 11 male and 12 female deaths, weight loss (15-38%), pallor, ascites, normochromic anemia, hyperleucocytosis and polynucleosis. AP level elevated in males, elevated serum BSP and AP values for females. Liver (m and f) spleen (f), adrenals (m and f) weights elevated, and uterine horns depressed. Ulceration in small intestine, ulceration and inflammation of intestinal mucosa, peritonitis, splenic hypertrophy and necrotic infarct, marked hematopoietic activity in the spleen red pulp, inhibition of spermatogenesis, and dilated kidney tubules.

DOGS: 3 MONTH:

Strain: Beagle

Route: Oral, capsule

Dose Level: 0, 3, 6, 12, 24 mg/kg divided into 2 doses.

Number: 4/sex/dose

Study Site: [REDACTED]

Results

3mg/kg: Slight increase in SGPT level and sedimentation rate, transient decrease in SA/SG ratio, increase in urobilin in urine, slight increase in BUN level, ulceration of the fundic mucosa with acute inflammation and edema of mucosa, jejunal ulcerations.

6mg/kg: diarrhea and melena, anorexia, weight loss, anemia, hyperleucocytosis and polynucleosis, albuminuria, bile pigments in urine, transient decrease in SA/SG electrophoretic ratio, urobilin in urine, gastric ulceration, congestive zones in small intestine.

12mg/kg: episodes of diarrhea, moderate increase in SGPT, urinary albumin, transient decrease in SA/SG electrophoretic ratio, increase in blood fibrin levels and sedimentation rate, absolute and relative weight of testicles low in one dog, gastric mucosal ulcers, seminiferous tubules devoid of germinal cells.

24mg/kg: 1 death day 12, diarrhea, melena, anorexia, weight loss (23%), erythropenia, anemia, hyperleucocytosis, bone marrow hyperplasia, slight elevation of SGOT, marked decrease in serum albumin and SA/SG electrophoretic ratio, blood fibrin levels markedly increased, sedimentation rate increased, ulceration of gastric mucosa, congestion and ulceration of jejunum and ileum, abnormal spermatogenesis.

BABOON: 1 year:

Strain: Papio cynocephalus and Papio anubis

Route: Oral, in gelatin capsules

Dose Level: 0, 4.5, 9, 27mg/kg/day Ketoprofen; 4.5mg/kg/day Indomethacin

Number: 6/sex/group

Study Site: [REDACTED]

Dosing commenced on 3/25/71. Two of each sex from each group were sacrificed after 6 months.

Observed Effects:

No clinical signs were seen which related to drug administration. Self inflicted bites were evident on forearms and lower legs of 3 low dose animals dosed with indomethacin.

Mortality:

One low dose male treated with indomethacin was found dead on week 47. Death was due to perforations in the stomach and peritonitis.

Body Weight/Food Consumption:

High dose group gained slightly less weight than other groups and particularly during the first 6 weeks. Appetite and water consumption were not effected by these dosages.

Hematology/Coagulation:

Though some animals had high or low hematology values at times, all results were not outside the normal range and were considered normal.

Blood Chemistry/Urinalysis

Several individual animals had values outside the normal range at various times, and normal values were obtained at times when further samples were analyzed. Urinalysis showed positive reactions for blood pigments at times in several animals.

Vital Signs/Physical Examination:

No ocular changes were seen that could be drug related. Isolated examples of fecal occult blood were observed during predosing and dosing period in all groups. Only F #208 showed consistently positive results in any one week.

Organ Weights:

Organ weights which were 10% lower than control weights were: pancreas, uterus, gonads (male) in low dose; spleen, uterus, thyroids, gonads (male) in mid dose; heart, pituitary, lungs, liver, spleen, pancreas, uterus, thyroids, gonads (male and female). Relative weights were within normal limits.

Gross and Histopathology:

Interim kills: mild mucosal congestion or minute dark-flecks in stomach mucosa of low dose; erosions in the mucosa of the pyloric antrum, congestion of the proximal duodenum, and hemorrhagic foci in the pyloric antrum of mid dose; mucosal congestion and erosion in pyloric antrum of the stomach and proximal duodenum in high dose.

1

•

2

3

Body Weight/Food Consumption/Water Consumption:

Mid dose males showed an increasing loss of mean weight gain (up to 10%) when compared to control males; the high dose females showed a mean weight gain difference of -21%. Food and water consumption did not differ from the controls.

Hematology

Blood was taken predose, and at 4, 8, 13, 26, 52, and 78 weeks in 10M and F from the control and high dose. At weeks 13 and 53, groups 2 and 3 were also studied and group 3 also at week 78. No low dose hematology parameters were significantly different from the controls when analyzed at weeks 13 and 53. No abnormalities were seen at week 13 in $WBC(F)$, $WBC(M)$, and neutrophils (F). The high dose group had depressed PCV, Hb, and RBCs throughout the study, while WBCs, neutrophils, lymphocytes, eosinophils, and platelets were elevated. Changes were mostly reported in the females.

Blood Chemistry/Urinalysis

Total serum protein was significantly low in both sexes at week 52 and 78, and was due to decreased albumin, α , or γ globulin levels. Other parameters differed significantly from control values at times and limited to one sex. Fecal occult blood was observed in 14 different rats beginning at week 6; however, most occurred during the 26th week and were in the high dose females. Blood was found on several occasions in the urine of some high dose rats. No other changes were observed.

Vital Signs/Physical Examination:

Eyes of all males and females in the control and high dose groups were examined (Keeler indirect ophthalmoscope) before treatment and at 4, 8, 13, 26, 52, and 77 weeks. Anterior synechia was observed in four males and keratitis was seen in five males in the drug treated group. These lesions did not occur in control animals at any time during the study. The sponsor states that "no changes attributable to treatment were evident."

Organ Weights:

Interim Kill: significantly different from control

Heart: high dose F, absolute weight

Spleen: M and F high dose, absolute and relative weights

Kidney: F low, mid, high, M mid, high, absolute weight

F low, mid, high, M low, mid, high, relative weight

Terminal Kill: significantly different from control

Heart: F high dose, relative weight

Pituitary: M high dose, absolute and relative

Brain: F high dose, absolute and relative

Adrenals: F mid, absolute

Liver: F low, mid, M, low, high dose, relative and absolute

Spleen: F mid, absolute, F mid, high, relative

Kidney: F low, mid, high; mid, high, absolute and relative

Gross Pathology:

Small Intestine: adhesion, congestion, nodules, pallor-mid and high dose
Kidney: enlarged, cortical scarring - low, mid, and high dose
Lymph nodes: enlargement in high dose

Histopathology:

GI tract: Jeal ulceration and inflammation in the adjacent mesentery (mid, high dose).
Kidneys: papillary necrosis (high dose), tubular degeneration (low, mid, high dose), interstitial fibrosis in the papilla (mid, high dose), cortex and medulla showed interstitial fibrosis and inflammatory cell infiltrations (low, mid, high dose)
Liver: necrosis of fibrosis (mid, high dose), congestion of centrilobular sinusoids (high dose).
Mesenteric lymph nodes: foci of cystic degeneration (mid, high dose)

The group incidence of renal lesions attributable to treatment was much higher in females which died during the study than in rats sacrificed at termination. Only in the high dose males which died during the study was this incidence higher than in rats killed at termination. Tumors not found in the controls include the following:

Pancreatic Islet cell adenoma: 1/11 high dose males histologically examined at termination.
Lymphoma: 1/27 high dose male and 1/30 high dose female histologically examined which died during the study
Papilloma: 2/27 high dose females histologically examined which died during the study
Other tumors were found in all groups of rats

RAT: CARCINOGENICITY STUDY - 91 WEEKS:

Strain: Sprague-Dawley, CD strain
Route: In the diet
Dose Level: 0, 3, 4.5, 7.0 mg/kg/day x 91 weeks*
Number: 60/sex/group
Study Site: [REDACTED]

*Dosing period was followed by a 13 week observation period. High dose males were killed after 89 weeks of treatment. Mid dose males were killed after 1 week in observation period.

Observed Effects:

Blood discolored urine or feces were observed on the paper beneath the cages of control and treated groups from week 25 onward. The incidence was higher in the mid and high groups. Palpable masses, reduced grooming, weight loss, and deterioration in the general conditions of the animals resulted from the treatment.

Mortality:

Treatment (mg/kg/day)	Incidence of Mortality							1-Termin
	1-26	27-52	53-78	Treatment Period (weeks)			92-104	
				79-89	79-91	79-92		
0 M	0	3.3	17	25	31	35	52	73 week
3.0M	0	6.7	38	40	46	51	53	85 week
4.5M	0	1.7	49	47	53	67	-	83 week
7.0M	0	8.3	58	57	-	-	-	83 week
0 F	1.7	0	12	-	19	-	50	65 week
3.0F	0	3.3	21	-	37	-	45	73 week
4.5F	0	6.7	29	-	26	-	41	72 week
7.0F	0	16.7	34	-	36	-	52	83 week

Body weight/Food Consumption/Water Consumption

Drug was mixed with food each week. Food intake of all groups was essentially similar, with drug groups varying by 2-4% from control. Slightly higher weight gains were recorded for the mid dose group compared with controls. Overall weight gain for high dose males through week 91 was significantly lower than control group. Water consumption was apparent in female high dose group in weeks 12 and 25.

Gross Pathology:

The following lesions appear to be treatment related and were seen in animals dying during the study and in animals that were killed.

GI tract: adhesions, discolorations, distentions, cysts

Stomach: discoloration, ulceration, adhesion, raised areas

Kidneys: cortical scarring, pale, enlarged/swollen, irregular surface, hydronephrosis, pelvic dilation, nodules.

Mesenteric lymph nodes: enlarged, congested, hemorrhage.

Liver: pale, discoloration, adhesions

Spleen: irregular surface, enlarged, adhesions

Urinary bladder: adhesions, congestion, thickened walls

Heart: ventricles thickened, pale flecking, nodular tissue

Histopathology:

Examination was done on adrenals, thyroids, ovaries, kidneys, liver, spleen, lymph nodes, duodenum, jejunum, ileum, bone marrow and pituitary plus all macroscopically observed lesions for every animal. Also brain, lungs, prostate, uterus, mammary gland and thymus from control and high dose (7.0 mg/kg). The following changes were treatment related.

GI tract: dose related ulceration/necrosis of small intestine, mostly in females area. Lesions considered major factor in cause of death.

Mesenteric and renal lymph nodes: cystic dilation increased in incidence in treated females at all levels and in high dose males.

Kidneys: dose related papillary necrosis (mostly females) with associated focal mineralization, acute pyelitis/pyelonephritis, chronic interstitial nephritis and dilation of renal pelvis. Progressive glomerulonephrosis was drug related. Kidney lesions were considered significant in the cause of death.

Other changes which occurred in one or more of the treated groups or at a higher incidence than in the controls are indicated below.

Liver: peritonitis and adhesion only in high dose females.

Adrenals: hyperplasia in treated females and high dose males; vacuolated/distended cells in cortex increased in treated females.

Adipose tissue: increased necrosis, fibrosis, mineralization, calcification, and cell infiltrations in treated males and females.

Cutaneous tissue: increased ulceration, necrosis, atrophy of hair follicles and sebaceous glands.

Heart: myocardial hypertrophy, fibrosis, inflammatory cell infiltration, thrombus/thrombosis, calcification, and pericarditis only in treated males and females.

Lungs: metaplasia in high dose males; mineralization/calcification in low and mid dose females.

Parathyroids: increased incidence of hyperplasia in both sexes of treated animals.

Spleen: extramedullary hemopoiesis in mid and high dose females.

Pituitary: slight increase in congestion and dilation of sinusoids in treated males.

Testes: increase in atrophic change/spermatogenesis inhibition in low and mid groups. A follow-up examination on the testes of all treated males and controls showed no statistical difference between treated and control animals.

Tumor Incidence

Doses

Control		Low		Mid		High	
D	T	D	T	D	T	D	T

No. of rats examined	43	16	49	9	47	10	45	10
No. of rats not examined due to advanced autolysis	1	-	2	-	3	-	5	-
No. of tumour bearing rats	27	12	33	5	21	5	17	7
No. of rats bearing more than one tumour type	9	5	7	2	6	2	4	1
No. of rats bearing malignant tumours	4	1	8	1	2	2	3	1

Females

No. of rats examined	38	21	44	16	43	17	50	10
No. of rats not examined due to advanced autolysis	1	-	-	-	-	-	-	-
No. of tumour bearing rats	35	15	38	16	32	16	32	10
No. of rats bearing more than one tumour type	18	7	15	11	14	12	15	7
No. of rats bearing malignant tumours	6	2	8	7	7	3	6	5

The sponsor should list the animal number, tumor type and week that the tumor was observed.

MOUSE: CARCINOGENICITY STUDY - 24 MONTHS:

These studies were conducted by [REDACTED]. The carcinogenicity of Ketoprofen (sodium salt) was evaluated in experiments 1, 2, and 3. The first experiment examined the toxicity of the drug in mice, while experiment 2 was used to determine the maximum quantity of the drug acceptable to the mice in their drinking water. Experiment 3 is the main carcinogenicity experiment. The sensitivity of the mice to 3,4-benzopyrene, a known carcinogen, was the theme of experiment 4.

The drugs were administered by gavage in experiments 1 and 4; in 2 and 3 the drug was dissolved in the drinking water. A stock solution of ketoprofen was prepared daily, diluted to appropriate concentrations, and supplied each day in glass bottles protected from the light. The volume of fluid not consumed was measured each day. In these experiments, batch #12CA0 198 was used to

prepare smaller batches HB 4213, HB 5083, and HB 5459. An inbred strain of mice, C57 B 1/6 Rho-Ico, was used in these experiments. The four experiments are described below.

Experiment 1

Dosage levels: 256, 128, 64, 0 mg/kg

Duration and Route: The mice were given 10 doses of the compound on days 1, 2, 3, 4, 5, 8, 9, 10, 11 and 12 by gavage. The surviving mice were kept under observation for 106 weeks.

Growth Effects: Body weights were checked for 51 weeks. The mean weights of the treated animals were slightly lower than those of the controls.

MortalityMortality (days) dead mice/mice in group

		1	3	4	5	8	10	11	12	18	26	30
Control	M											0/20
	F											0/20
1/2 kg	M											0/20
	F									1/20	1/20	1/20
5/2 kg	M		1/20	1/20	1/20	6/20	7/20	7/20	7/20	7/20	7/20	7/20
	F									1/20	2/20	2/20
5/2 kg	M		2/20	11/20	14/20	20/20						
	F				1/20	10/20	11/20	12/20	13/20	13/20	13/20	13/20

The drug was more toxic to the male animals than to the female animals.

Histopathology:

No toxic effects were noted on histological examination. Statistical analysis of lymphoreticular system tumors which were found fairly frequently, revealed no difference between the control and treated groups. The statistical analysis used by the firm was the Fisher's exact method (unilateral test).

Experiment 2

Number of animals/level: 20M and F/level

Dosage levels: 64, 32, and 0 mg/kg P.O.

Duration and Route: The drug was given for 43 days in the drinking water. The animals were kept under observation for 21 weeks after the start of treatment.

Results: This experiment was to determine what the maximum concentration in the drinking water should be in order to obtain a dosage of 32 mg/kg, which was the maximum dosage selected for experiment three. The consumption of the drinking water was much lower in the 64 mg/kg a group, especially in the female animals. The mean weights of the treated animals paralleled those of the controls.

Experiment 3

Number of Animals/level: 50M and 50F/level.

Dose levels: 32, 0 and 16, 8, 4, 0 mg/kg p.o.

Duration and route: The drug was given for 105 weeks in the drinking water. Water consumption was almost constant at 4 ml/mouse/day.

Results: Mean weights of M and F treated animals were slightly lower than the mean control weights. Statistical analysis by the firm revealed no difference between the three most frequently occurring tumors in the treated animals and the control animals. Rare tumors were found in all groups. Tumors of the lymphoreticular system (LRS) and of the Eussey-Guerin type did not appear at a different rate in the treated mice when compared to the controls. Non-tumor lesions were of inflammatory origin and appeared not to be drug related. The presence of renal papillary necrosis was observed in 2M and 1F in the high dose group and may be drug related. Ophthalmology examinations, hematology, blood chemistries, and urinalysis were not performed. Tables 1 and 2 indicate the number of animals sacrificed for necropsy vs. time and the type and number of tumors found on histological examination, respectively.

TABLE I

Table 1. Tumor Incidence in Mouse Carcinogenicity Study of Ketoprofen

Doses		Controls		32 mg/kg		16 mg/kg		8 mg/kg		4 mg/kg	
Sex		M	F	M	F	M	F	M	F	M	F
Tumors of the lymphoreticular system	Benign:	2	1	3	2	1		2			
	Malignant:										
Hepatomas	(1) lympho, reticulo, histiocytosarcomas, sarcomas, osteosarcomas, leukosarcomatosis	30	50	12	26	14	23	11	30	15	29
	(2) malignant Koussey-Guérin reticulosarcomatosis	7	5	1	2		3	2	3	2	3
Lung tumors	Adenomas	6	1	3				1	1	2	1
	Adenocarcinomas										
Tumors of the endocrine glands	Pituitary adenomas	1	2	2	1	2		3	1	3	
	Thyroid adenomas	1		1		1					
Soft tissue sarcomas	Parathyroid adenomas	4		1		2					1
	Fibrosarcomas		1								
Adenocarcinomas of undefined origin	Undifferentiated sarcomas										
	Histiocytosarcomas			1				1		1	
Others (benign tumors and psuedo-tumors)	Lipoma	1	2	1		1				1	3
	Adenocarcinoma of mammary gland		1					1			
	Angiomas	1						1		1	1
	Spleen*	7	1	1	1	1	2	1	1	1	1
	Ovaries							1			
	Uterine polyps		1					1			
	Cholesteatoma										
	Adenoma of the salivary glands				1						
	Adenoma of the biliary tract	6	7	5	8	7	4	1	5	7	2
	Papillomatosis of bladder										
Number of animals examined		96	97	49	48	50	47	45	49	45	49

(*) In male mice treated with 16 mg/kg orally, the only tumor reported corresponds to the hemangioendothelioma which was found in 1 mouse.

N-18754-4

Experiment 4

No. of Animals/level: 50M and 50F/level

Dosage levels: 500 and 0 mg/kg

Duration and Route: The animals were given 32 doses of 3, 4-benzopyrene (a known carcinogen) at a level of 500 mg, then 250 mg/kg p.o. by gavage. The compound was in the form of a fine suspension in distilled water. The total amount of drug administered to the animals was 14.75 g/kg. Control animals received only 25 mg/kg p.o. distilled water. Surviving animals were sacrificed in the 80th week.

Results: Treatment was interrupted several times due to unsatisfactory weight gain and poor condition of these animals. The first 27 dosings were at 500 mg/kg and the last five treatments were at 250 mg/kg.

Epidermoid cancers of the non-glandular part of the stomach (24/40 M, 60% and 16/39 F, 41%) occurred with a high incidence. Only one case of this tumor was found in the F control group (1/50 F, 2%). The other location of high tumor incidence was the lymphoreticular system (M=25%, Control=20.8%; F=59%, control=16%). This is a highly significant difference ($p=0.0004$) in the female. These LRS and Roussy Guerin tumors appeared at a greater rate in the treated animals, when compared to the control mice.

Evaluation of experiments 1 through 4: In experiments I and III the distribution and incidence of tumors were considered normal for all groups when compared to the controls. Animals treated with 3,4-benzopyrene (experiment 4) showed a greater incidence of LRS and Roussy-Guerin tumors when compared to the control animals. Females in this group developed these tumors at a significantly greater rate than the males or the control. In general, Ketoprofen is more toxic in the male mouse than in the female.

In experiment 3 no significant difference was observed when statistical analysis (Fisher's exact method, done by Rhone-Poulenc) was done on the three types of tumors which occurred most frequently, i.e., malignant tumors of the lymphoreticular system hepatomas, and adenomas of the biliary tract. Only in the 5 mg/kg females group did the incidence of tumors of lymphoreticular system and of the Roussy-Guerin type appear somewhat earlier than those of the control females.

REPRODUCTION:

Segment I: Fertility and General Reproductive Performance Rat

Strain: CD (COBS), Charles River, France

Route: gavage - 2 divided doses/day in the mid and high groups

Dose: female - 0, 3, 6, 9 mg/kg/day x 4-5 weeks - 2 weeks pre-mating

male - 0, 3, 6, 9 mg/kg/day x 67 (pre-mating) + 6 days during mating

Number: 36 females/16 males/dose level

Study Site: [REDACTED]

Six dams (17%) in the high dose group died; one death was accidental. No deaths in the other female groups. GI lesions were found in 2/6 deaths. Mean implantation sites were significantly ($p = 0.05$) low in the mid and high dose groups. The mid dose group also had a significantly low percentage of pregnancies and a significantly high number of resorptions when compared to the control values.

Seven males died during the study 6 high dose and 1 mid dose. GI lesions were seen in 4/6 which died. Ketoprofen did not have any effect on the general reproductive function of male rats treated with 3, 6, or 9 mg/kg/day. Mid and high groups had "Sertollian Involution" affecting a few isolated seminiferous tubules, but rats thus affected were not infertile.

SEGMENT II: TERATOGENIC ACTIVITY

Mouse:

Strain: Charles River France, CD, (COBS)

Route: by gavage

Dose: 0, 3, 6, 12 mg/kg/day from day 5 through day 15 of pregnancy at 25 ml/kg of body weight (1.2% solution of Na salt). Mid and high doses were administered in divided doses at 3 hr interval daily.

Number: 20 females/dose level

Study Site: [REDACTED]

No animals died. The percent of pregnant was lower in the drug treated animals than in the control but was not significant. The number of pups that died during the first month was about the same in the treated groups (low 13%, mid 17% high 14%), but was 2-3 times higher than in the control (6%); these differences were said not to be significant, however. No embryotoxic effects or significant damage to the postnatal development of the pups were observed, not a single malformation was found in the mice examined at birth or at 30 days.

Rat:

Strain: Charles River France, CD (COBS)

Route: by gavage

Dose: 0, 3, 6, 9 mg/kg/day from day 5 through day 15 of pregnancy at 5ml/kg of body weight. Mid and high doses were administered twice a day at a 3 hour interval.

Number: 20 females/dose level

Study Site: [REDACTED]

In a preliminary study, 4/6 treated rats (12 mg/kg) died by day 6-8 due to peritonitis and GI ulcers. The two surviving pregnancies proceeded with no problems.

In the main study 7/20 high dose rats died after 4-6 days of dosing (peritonitis and intestinal ulcers). No other deaths were reported. A very slight decrease in average weight gain occurred in the high dose. No change observed in the percent of pregnant rats in the treated groups, in the average number of implantation sites, number of resorptions, still births, or average weight of living fetuses. A slight decrease was seen in the average number of living fetuses in the mid and high dose groups. The male/female ratio was also slightly changed in the high dose (0.80) and mid dose (1.2) when compared to the control (1.0). Cranioschisis (0.8%) was observed in one high dose rat; no other teratogenic effects were reported.

Rat:

Strain: OFA (Specific Pathogen Free)

Route: Intramuscular (each leg)

Dose: 0, 3, 6, 7.5 mg/kg (1 ml/kg, days 5-15 of pregnancy) as the sodium salt.

Study Site: [REDACTED]

Toxicity (GI ulceration and peritonitis) resulted in the death of 3/22 high dose rats by days 9-10. No other deaths occurred. This study showed no evidence of embryotoxicity effect of growth on the fetuses in utero, or teratogenicity.

Rabbit:

Strain: Fauve de Bourgogne - 20/dose level
Route: administered orally
Dose: 0, 3, 6, 12 mg/kg/day, day 6-28 of pregnancy. Mid and high doses were administered twice/day at a 3 hour interval at 1ml/kg
Study Site: [REDACTED]

One control death at day 28 and 2 high dose deaths at days 9 and 15. Deaths in the treated animals were due to peritonitis and GI ulcers. A significant body weight loss was seen on day 16 in the high dose group. The average number of implantation sites decreased (5%) in the high dose group when compared to the control. Likewise, a large significant ($p = 0.01$) increase in the percent of resorptions was seen in the mid (22.7%) and high dose (23.9%) groups when compared to the control (7.9%); the low dose was slightly increased (12.1%). A significant decrease ($p = 0.05$) in the average number of living fetuses occurred in the mid and high dose group. The male/female ratio in the drug groups was reversed compared to the control. Low dose pups showed a significant decrease in the number of pups under 20g in weight. The presence of a face deformation, with incomplete development of the jaws and surrounding tissues, was seen in one pup from the mid and high dose groups. This deformation was not observed before in this strain of rabbit and could be drug related. The number of abnormal fetuses were control 2, low dose 1, mid dose 7, and high dose 5.

Rabbit:

(Complementary Study)

Formulation: aqueous solution of sodium salt
Dose: 0, 3, 6, 12mg/kg/day from days 6-16 of pregnancy. For the control, mid, and high dose administration was divided at an interval of 3 hours. Control received distilled water.
Route: oral (gavage)
Species: Fauve de Bourgogne
Number: 16-18 pregnancies/group
Study Site: [REDACTED]

GI lesions were produced in 2-3 animals in each dose level. No deaths were seen in the control and high dose groups. The low dose contained one death (day 15) and the mid dose contained 3 deaths. (2 deaths and 1 sacrifice). Food consumption and body weight gain were reduced in the mid and high dose groups. The percentage of resorptions was significantly greater and the mean number of live pups/litter was lower in the high dose group. The only skeletal malformation in the treated animals was the fusion of 2 ribs in one mid dose pup; one control pup showed lung atrophy/hypertrophy and an abnormal appearing liver. This study tends to indicate the absence of teratogenic effects in this species of rabbit under the conditions of the study.

Rabbit:

Strain: NZW 2.8-4kg, 19-20/group

Route: oral, in gelatin capsules

Dose: 0, 2, 4 mg/kg/day from day 6-16 of pregnancy.

Study Site: [REDACTED]

One 2 mg/kg animal died on day 4- no other deaths were noted. Statistically significant maternal weight gain and food consumption were reduced in the high dose. The low dose showed the same trends, but were not significant. Likewise, the numbers of dead and resorbed fetuses were higher in the treated groups and significant in the high group. The mean number of fetuses/litter was 20% lower than the control, but was not significant. One abnormal fetus (truncus arteriosus) was found in the control, three abnormal fetuses (double gallbladder bilateral cataract, and flexed wrists) in the low dose, and one abnormal fetus (unilateral cataract) in the high dose. One dead fetus in the low dose had 2 abnormalities; absence of abdominal muscle which had been observed in control animals, and a cardiovascular effect which had not been seen before.

Rabbit:

Formulation: aqueous solution of sodium salt with 2 1/2% benzyl alcohol
Dose: 0, 1.5, 3mg/kg/day at 1ml/kg of body weight from day 6 through day 16 of pregnancy

Route: Intramuscular

Species: NZW rabbits

Number: 15-17 primiparous females/group

Study Site: [REDACTED]

One low dose was found dead on day 17. The cause of death could not be determined. No other deaths were reported. Under the conditions of this experiment no embryotoxic effects, no effect on growth of fetuses in utero, and no teratogenic effects were observed.

Segment III: Perinatal and Postnatal Study

Rat:

Formulation: suspension of ketoprofen in 0.5% gum tragacanth

Route: oral (gavage)

Dose: 0, 3, 6, 9 mg/kg/day from day 15 of gestation through lactation to 21 days post partum, * 12/dose

Species: Charles River France (CD, COBS)

Study Site: [REDACTED]

*For comparison three further groups of rats received Indomethacin at 1.5, 3, and 6mg/kg/day.

Mortality:	Group:	0,	3mg/kg	6mg/kg	9mg/kg
	Deaths:	1/12	2/12	2/12	8/12

Animals died or were killed before, during, or after parturition. All high dose indomethacin animals died or were killed, prior to parturition. Autopsy showed fibrous adhesions between the liver and GI tract. In high dose Ketoprofen survivors, delayed or incomplete parturition was seen in 2/4; the mid dose incidence was 5/7, the low dose was 1/10, and the control was 1/9. Total litter loss occurred in 3 high dose Ketoprofen dams. Litter and mean pup weights for the low dose Ketoprofen were comparable to the control, with the mid dose pup weight slightly lower than the control at birth. High dose mean pup weight at day 21 was about 10% below the control value. No abnormal pups were observed in this study.

SPECIAL STUDIES:

Mutagenic Potential:

Ketoprofen (41.9, 21, 10.5, 5.2, 2.6 μ mole/plate) showed no mutagenic activity when tested against strains of *Salmonella typhimurium* (TA-100, TA-98, TA-1535, TA 1537, TA 1538), both with and without added S-9 from mice, rats, or hamsters. Benzpyrene at 5 μ g/plate was mutagenic only in the presence of S-9 fractions.

Cytotoxicity Activity:

At a concentration of 4 mg/ml, Ketoprofen was cytotoxic to cultured KB cells (human oral carcinoma line). This is 500-1000 times greater than that found in the blood of patients treated with the drug.

Local Tolerance Tests:

No irritating action of a solution of the drug was observed in the ocular or cutaneous tolerance test in rabbits. I.V. or intra-arterial tolerance studies in rabbits produced redness and edema, while a paravenous test was poorly tolerated locally. The latter was partially caused by the vehicle (aqueous benzyl alcohol). Concentrations of 1% or higher of the sodium salt were poorly tolerated in intra spinal studies in the rabbit. At this level toxic changes in the CNS were observed and death was produced in 1/6 animals. In dogs, both the intramuscular and intraarticular injections of ketoprofen were well tolerated.

Toxicity of Related Compounds:

The acute oral toxicities in mice of four intermediate compounds is given below.

Ketoprofen	-CH(CH ₃)CO ₂ H	950
RP23,642	-CH ₂ Br	1,000
RP23,643	-CH ₂ CN	200
RP23,644	-C(CH ₃)(CN)CO ₂ Et	620
RP23,731	-CH(CN)CO ₂ Et	1,000

The acute toxicity values after oral administration to mice were established for 4 impurities found in ketoprofen. The impurities and their LD50 values are as follows:

	R =	LD50 (mg/kg)
RP 19,421	-CH ₂ CO ₂ H	898 (a)
RP 22,551	-CH(CH ₃)CONH ₂	641 (b)
RP 24,336	-CH(CH ₃)CN	210 (b)
RP 33,601	(4-methylbenzoyl)-3-phenyl-2-propanoic acid	900 (c)

- (a) hypomotility, dyspnea, convulsive fits.
- (b) decubitus with dyspnea, loss of righting reflex
- (c) hypokinesia, hyperesthesia, sedation

ADVE STUDIES:

Absorption:

Rat

Plasma T 1/2 = 6 hours and 18 hours (2 phases) in males. Serum levels were 0.15 - 0.2 mg/ml after 1 hour with a single dose of 100 mg/kg of Ketoprofen. The major circulation compound at this time was unchanged Ketoprofen. Absorption of the sodium salt produced similar result. In weanling females and adult females the peak plasma level was reached in 1 hour after 1mg/kg. T 1/2 = 3 and 12 hours in weanlings, and T 1/2 = 8 hours in the adult females. Other studies showed that a 5 day pretreatment did not alter catabolism by enzyme induction binding to serum proteins was relatively labile.

Rabbits:

Peak concentrations of unchanged drug ranged from 4.2 to 16.4 mg/l one hour after drug administration. At 24 hours the serum level was 0.22ug/ml.

Dog:

T 1/2 = 0.85, 4.3, and 34 hours. Peak plasma levels occurred at 2 hours (5-7 mg/l from 5 mg/kg dose). The oral absorption of the drug from Orudis capsules ranged from 75-93% in 4 different lots tested. When lactating females were studied, the level of ketoprofen in the milk was about 4-5% of the serum concentration.

Monkey:

Peak plasma levels of 1.6 and 0.84 were reached in one hour after a single oral dose of 2mg/kg or i.m. dose of 1mg/kg, respectively. Disappearance from plasma followed biexponential curves: half-lives were 1 hour and 29 hours for the oral route and 1 hour and 35 hours for the i.m. route. Noncoated capsules (2 mg/kg p.o.) and rectal suppositories (4 mg/kg) produced maximum average plasma levels at 1 hour of 1.6mg/l and 2.65 mg/l, respectively. Maximum levels were achieved at 3 hours with the enteric-coated capsules (0.8 mg/l) and remained high for 6 hours (0.49 mg/l).

Distribution:Rat:

Tissue distribution was studied only in male rats. The distribution of the total radioactivity following the administration of 1mg/kg is indicated in the following table.

% of the radioactivity administered			
	8 hours	30 hours	4 days
viscera, skin			
carcass and plasma	40.7	7.2	1.2
urine (cumulative)	24.2	42.0	54.0
feces (cumulative)	27.5	46.0	45.0
Total radioactivity	92.4	95.2	100.2

The 8 hour distribution in the viscera, skin, carcass, and plasma was as follows, (% of total radioactivity)

Brain 0.025	Genital tract 0.740	Intestine 54.45
Spleen 0.065	Kidney 4.920	Skin 8.81
Heart 0.100	Stomach 6.200	Carcass 12.05
Lung 0.170	Liver 7.180	Plasma 5.29

The disappearance of ketoprofen from the tissues and plasma were each characterized by 2 half-lives, the longer of which was similar for both plasma and tissues.

Metabolism:

The biotransformation of Ketoprofen was examined in the urinary, fecal, and biliary extracts from dogs, rats, rabbits, and monkeys, and the urinary extracts from humans. Metabolites were classified in order of increasing polarity, A,B,C,D,E,E₁,F, G₁, and G₂.

E rat, monkey.

E₁ rat,

F rabbit

The comparative urinary metabolites of ketoprofen is indicated in the table below.

Product	Dog	Rat	Rabbit	Monkey	Man
A	not detected or traces	not detected	traces to +	not detected	not detected
B	→	→	→	→ to →	→ to →
C	not detected or traces	+ to →	not detected	→ (c)	+
D		→		traces to +	-
E		+ to → (a)		traces to + see C	not detected
F		traces to + (b)		not detected	
G	→ to → (d)	not detected not detected not detected to + (a) (d)	+ to → → (d)	not detected + (d)	
					G ₁ → to → G ₂ + to →

(a) depending on the individual

(b) depending on the sampling delay

(c) + probably product E₁

(d) probably product G₁

The urine was a major route of excretion for ketoprofen and its metabolites in all species tested. Bile and feces also contained measurable levels of untransformed ketoprofen; however, the rat and possibly the dog were the only species which showed significant excretion by these routes. Conjugation with glucuronic acid predominates in dogs, rabbits, and man, while hydroxylation was the major metabolic path in rats and monkeys.

Excretion:

Rat:

After 1mg/kg dose, at 30 hours the urine contained 42% of the administered dose and the feces contained 45%. The parent drug was 15-20% in the urine and 10% in the feces. Four days after drug administered only 1% of the original dose remained in the animal. Both drug and metabolites are involved in a significant enterohepatic cycle.

Rabbits:

Urinary excretion amounted to 10-43% over the first hours after an oral dose of 5mg/kg. Less than 1% was excreted in the feces, and biliary excretion was minimal (10 mg/l after 6 hours).

Dogs:

Over 6 days, 35% of the administered dose (1, 3, or 100mg/kg) was excreted in the urine, with 15-32% being unchanged Ketoprofen. Fecal excretion was about 1-5% of the total dose over the first two days.

Monkey:

About 72% of an administered dose (2mg/kg) was excreted over a 6 day period, with most of the excretion occurring in the first 24 hours. Unchanged drug accounted for 87% of the excreted radioactivity. Urinary excretion was almost complete within 24 hours with several formulations, i.e., entericoated, non coated, l.m., or suppositories.

INVESTIGATOR'S BROCHURE/PACKAGE INSERT:

Comments on the package insert will be postponed until the items in the recommendations have been completed and reviewed.

RESULTS AND DISCUSSION:

Orudis (Ketoprofen) is a nonsteroidal anti-inflammatory drug indicated for acute or long term treatment of musculoskeletal and soft tissue inflammatory conditions, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, and acute painful shoulder syndrome. The maintenance dosage for chronic conditions is 100mg t.i.d. or 100-200 mg b.i.d.

Extensive pharmacologic and toxicity studies have been done in four species. Reproduction (segments I, II, and III), mutagenicity, ADME, and carcinogenicity studies in mice (18 months) and rats (21 months) have also been done.

The oral LD₅₀ is 360mg/kg in mice, 160mg/kg in rats, 1300mg/kg in guinea pigs, and greater than 1000mg/kg in dogs. In acute toxicity studies, mobility, ataxia, diarrhea, bradypnea, anorexia, weight loss, and ulcers were observed in two or more species. In addition, rats also showed peritonitis, intestinal adhesions, and respiratory failure, while dogs showed emesis, tachycardia, polyuria/dark urine, and loose discolored stools.

In subacute and chronic studies, anemia (decrease in Hb, RBC, MCV, and PCV) developed in the rat, dog, and baboon. The WBCs were elevated in the rat and baboon, and elevated urinary bile salts were seen in the rat, dog, and baboon. BUN, SGOT, and SGPT were elevated in the dog, while alkaline phosphatase was elevated in the rat. A decrease in the serum albumin/globulin ratio occurred in the dog - the rat showed a decrease in the serum protein value. The histopathology revealed g.i. ulcerations in the rat, dog, and baboon, and kidney papillary necrosis in the mouse, rat and baboon. The baboon kidney also developed congestion of the medulla and hemorrhage. In addition the rat kidney also showed tubular degeneration, glomerulonephrosis, and dilated cortical or medullary tubes. The rat liver showed ulcerations inflammation, necrosis, and fibrosis. Other toxicity occurring in the rat was bone marrow hyperplasia, cystic degeneration in the renal and mesenteric lymph nodes, adhesions, and peritonitis. The target organs for toxicity are the g.i. tract, kidney, and liver.

Segment I study in the rat indicated a slight decrease in the number of implantation sites in the mid (6mg/kg) and high (9mg/kg) groups. Mid dose animals also had a significantly lower percentage of pregnancies, and implantation sites were significantly higher. No effect was observed on the general reproductive function of the male rat when given 3, 6, or 9mg/kg of Ketoprofen.

Segment II studies showed no teratogenic activity in the mouse (3, 6, 12mg/kg, p.o.), in the Charles River CD1 rat (3, 6, 9mg/kg, p.o.), or in OFA rats (3, 6, 7.5mg/kg i.m.). In the Fauve de Bourgogne rabbit (3, 6, 12mg/kg, days 6-28 of pregnancy) a face deformity, not seen before in control animals, was observed in one mid and one high dose groups. There was also an increase in the number of abnormal fetuses in the mid and high dose groups. In a complementary study in this strain (3, 6, 12 mg/kg, days 6-16 of pregnancy), no teratogenic effects were observed; however, resorptions were significantly higher and the number of live pups per litter were significantly lower in the high dose groups. In NZW rabbits (2, 4 mg/kg, p.o., days 6-16 of pregnancy) one low dose fetus which died, had a cardiovascular effect which had not previously been seen. When ketoprofen was administered by the i.m. route to NZW rabbits (1.5, 3 mg/kg, from days 6-16 of pregnancy), no teratogenic effects were observed.

A Segment III study in the rat (CD, COBS at 3, 5, 9mg/kg) produced a high mortality rate in the 9mg/kg group (8/12). Survivors in the mid and high groups had delayed or incomplete parturition. Litter and mean pup weights for the low dose animals were comparable to the control. Mid and high dose pups were lower in weight. No abnormal pups were observed in this study.

The drug showed no mutagenic activity in the Ames test. At 4mg/ml it was cytotoxic to cultured KB cells but showed no anti-tumor activity against grafted tumors in mice.

In a 2 year mouse carcinogenicity study (4, 8, 16, 32 mg/kg/day x 105 weeks), no relation was seen between the administration of ketoprofen and the occurrence of the three types of tumors most frequently observed. The primary tumors found in the 91 week carcinogenicity study in Sprague-Dawley (CD) rats (3, 4, 5, 7mg/kg/day x 91 weeks; in the diet) were pituitary adenomas in both sexes and mammary gland adenomas, adenocarcinomas, and fibroadenomas. Adenocarcinomas of the small intestine were not statistically significant from the control. In this study, a time-course graph of the incidence of the major types of tumors, as well as a tabulation of the animal numbers, the type of tumor and week of death will be required for further evaluation.

ADME studies were conducted in rats, rabbits, dogs, and monkeys. Peak plasma levels occurred in the rat at 1/2 hrs and 2hrs (2 phrases). In dogs the peak level occurred at 1-2 hrs, and at 1 hour in the monkey and rabbit. Plasma half-life was 6 and 18 hours in the rat, 0.85, 4.3, and 34 hours (3 phrases) in the dog, and 1hr and 29 hours in the monkey. Binding to plasma proteins was relatively labile. Distribution of ketoprofen and its metabolites in male rats was mainly in the intestine, stomach, liver, kidney, carcass and plasma. Ketoprofen was also found in the milk of lactating dogs. The major metabolites in the rat were C, D, and E. The dog produced B and G. Man metabolizes ketoprofen to B, C, D, and G (G₁ and G₂).

The urine is the major route of excretion for ketoprofen and its metabolites in all species tested. The rat and dog were the only species which showed excretion by way of bile and feces. Only 1% of the drug remained in the rat four days after administration of 1mg/kg.

The pharmacological and toxicological profile of ketoprofen has been extensively studied. Major organs which showed toxicity were the gastrointestinal tract, kidney, and liver. Anemia was also produced in several species. Ocular toxicity was not observed. There is no indication that ketoprofen has a carcinogenic potential under the conditions studied in the mouse. With this submission, the suggested preclinical studies have been completed; however, before recommending approval of this NDA the reviewer would like the sponsor to respond to the questions in the following section which relate mainly to the rat carcinogenicity study.

RECOMMENDATIONS:

The following items are for transmittal to the sponsor:

- 1) In the rat two year carcinogenicity study, please list all rats that had tumors and all rats that died from causes either related or unrelated to tumors, including the name of the tumor and the cause of death. Rats should be listed week, dose, and sex.
- 2) Please explain the testicular tubular adenoma reported in one ovary in animal #182 of vol. 1.64, pp 113 and 230.
- 3) Table 3.7, p. 171 of vol. 1.1 indicates one high dose female with adenocarcinoma of the pancreas, but this is not indicated in Table 10, p. 64 of volume 1.68.
- 4) Table No. 1 a, p. 225 of vol. 1.65 indicates litter weights of rabbits; however, the study is concerned with the teratogenicity in rats by the i.m. route.
- 5) Pages 290 and 291 are missing from vol. 1.69.
- 6) Reference is made to an oral LD50 of 145mg/kg in rabbits and LD50 2000 mg/kg in dogs. These data are not found on Table 3.1, p. 131 of vol. 1.1. Please indicate the study in which these values were determined.

A.W. Coulter

A. W. Coulter, Ph.D.

cc:

Orig. NDA 18-754

HFD-150, HFD-180

HFD-150/AWCoulter:6/16/82

HFD-150/CSO/DMoore

F/D endorsed by DJRichman

F/F deg:7/29/82 8715A

W. J. J. J.
8/10/82

mor

deleted the following statement should be added "Abnormal spermatogenesis or inhibition of spermatogenesis developed in rats and dogs at high doses and a decrease in weight of the testes occurred in the dogs and baboons at high doses".

4. Page C

Methotrexate and Lithium interactions are appropriate and should be included.

5. Page D

Dosage and Administration Section

Add "In Rheumatoid Arthritis and Osteoarthritis the recommended dose etc." in the first paragraph.

In the last paragraph, I would prefer that the pain and dysmenorrhea sections be separated. In mild to moderate pain initially 50 mg every 4 to 6 hours is recommended. If the response is unsatisfactory then a trial of 75 mg every 4 to 6 hours is warranted.

In dysmenorrhea the recommended dosage schedule is 50 to 75 mg q.i.d. It is suggested that initially 50 mg q.i.d. be tried and if symptomatic relief is insufficient then a dosage schedule of 75 mg q.i.d. be recommended. Some patients have shown prolonged benefit from an initial loading dose of twice the regular dose.

The above comments as well as those of other reviewers should be incorporated into the FPL.

II. Review of First Periodic Report

This represents experience with the first 3 months of marketing. Approximately [REDACTED] No adverse events are submitted. The literature survey does not include new material of interest to the revision of the package insert.

III. Summary

In the original MO review of the ketoprofen analgesic data, two issues were raised. First was the population of the 2 chronic dose studies and the rates of events in these studies. The patients in the chronic studies were "scavenged" from other studies i.e. they were patients previously exposed to and shown to be tolerant of ketoprofen who were then enrolled in the "new"

studies and assigned different numbers. It was unclear from the data if the duration of exposure was dated from the enrollment in the "new" study or from the date of enrollment in the original study. Thus the emergence of events (particularly p.u.) by duration of exposure was unclear. The rate of occurrence of p.u. was high (around 4%). A possible explanation for this rate was that it was an artifact and reflected a longer duration of exposure than that accounted for by limiting duration of exposure to the "new" studies rather than total exposure accumulated over participation in 2-3 studies. The submission of 3-18-86 addresses these concerns but does not really explain them (See GLR 8-5-86). The most likely explanation for the higher than expected rate of p.u. is that it represents cumulative risks over longer periods than those accounted for in the original submission.

The second issue was the dosage schedule in the dysmenorrhea studies. I feel this needs further definition. I don't think it is a major issue i.e. one preventing approval. The recommendations in the label are "reasonable". However it is still unclear if an initial loading dose is necessary or of sufficient benefit to justify the "risks". While it can reasonably be inferred that 50 mg is effective (25 and 75 mg are), it would be preferable to establish the effectiveness of this dosage schedule and the benefits, if any, of this regimen in comparison to those of the 75 mg dose.

Therefore we should ask as a Phase IV requirement that they perform a study demonstrating the effectiveness of the 50 mg dose and the benefits, if any, of an initial loading dose of 2x the regular dose. The company has had success with dysmenorrhea studies in the past and I do not anticipate great difficulties with this request.

Recommendation

1. The changes in the label requested in this review and the GLR of 8-5-86 should be conveyed to the sponsor.
2. We should request a Phase IV dysmenorrhea dosing study as described.
3. We should request the additional analyses defined in the GLR of 8-5-86.

Eileen F. Barker 8/7/86

Eileen F. Barker, M.D.

cc: Orig NDA 18-754

HFN-150/Div File

HFN-150/Barker

HFN-150/Pease

HFN-340

D/T by P. Amoss/8/5/86

D/T by P. Amoss/8/6/86

F/T by P. Amoss/8/7/86

Wang #3487J

[Handwritten signature]
See GLR
8-7-86

gBalm...
8-29-86

Medical Officer Review

NDA 18-754/5003

DEC 30

NDA 19-397

Name of the Drug: Orudis
ketoprofen

Analgesic Dosage Schedule of Ketoprofen

The efficacy and relative efficacy of ketoprofen at different dose levels is organized in the attached table (pp. 35 & 36 of the original MO review). It may be summarized briefly as follows:

Ketoprofen 25 mg was statistically significantly more effective than placebo in dental pain (Cooper - 376, Attachment A; Mehlich - 374, Attachment B), post-partum pain (Sunshine - 375, Attachment C; Kantor - 377, Attachment D), dysmenorrhea (Lamb - 349, Attachment E & F). Ketoprofen 25 was numerically better than ASA 650 mg in Cooper 376, and statistically significantly better than codeine 90 mg in the Mehlich 374 study but not in Kantor 377.

Ketoprofen 50 mg was statistically significantly more effective than placebo in dental pain (Mehlich 374, Cooper - 376), post-partum pain (Sunshine 375, Kantor 377), post-operative pain (Sunshine 398, Attachments G & H). Ketoprofen 50 mg was statistically significantly more effective than ASA 650 mg in Cooper - 376, Mehlich - 374, Sunshine - 375. At this dose ketoprofen was significantly more effective than codeine 90 mg Mehlich - 374, and equivalent to ASA 650/Cod. 60 in Honig 399, Attachment I and J. *J. H.*

It seemed from the evidence that ketoprofen 25 mg while unquestionably more effective than placebo was not consistently significantly better than the standard agents. Ketoprofen 50 mg was more clearly in the prescription analgesic range, was significantly superior to ASA 650 mg, superior to codeine 90 mg and at least equivalent ASA 650/Cod. 60. From the "relative" efficacy status it seemed that ketoprofen 50 mg was the appropriate dose for a prescription analgesic - in that one expects greater relief from prescription products than is provided by OTC products.

Ketoprofen 25 mg is more effective than placebo and may be appropriate for "maintenance" analgesia. However, in dysmenorrhea the available evidence suggests that 25 mg. is not the appropriate dose. On a dosage schedule of 25 mg q.i.d. the immediate relief of symptoms was comparable to 75 mg. q.i.d. but by 4 hours it was approaching placebo and by bedtime was indistinguishable from placebo. This effect was present with diminishing intensity over the 3 days of treatment. Clearly 75 mg q.i.d. was the optimum schedule in that it gave relief of symptoms in the immediate post dosing phase which persisted throughout the day and was still present in the morning. The data suggests that ketoprofen 25 mg. gives acute short-lived symptomatic relief but that this effect is not maintained over the duration of dysmenorrhea symptoms and would not be acceptable to patients. As noted before it was unfortunate that 50 mg was not tested in

dysmenorrhea. I think there is enough data from the non-dysmenorrhea studies to infer that 50 mg is effective in dysmenorrhea and that it is appropriate to start at this dose. We should also note in the label that in dysmenorrhea a dosage of 75 mg. q.i.d. has been shown to be effective, (more effective than ibuprofen 400 mg.) and appears well tolerated.

I think the lack of discrimination between high doses of ketoprofen (50, 75, 100 mg) does not necessarily mean that there is no real difference in effect but rather suggests that the studies may have lacked sufficient upside sensitivity to detect such differences.

In rheumatoid and osteoarthritis the effect of 25 mg. is not well defined. Two studies in RA provide some experience. In study MSD 201, subjects were originally placed on 50 mg. q.i.d. with permitted switch to 25 or 75 mg. q.i.d. depending on their response to the original dose. 115 subjects were "switched" to 25 mg. q.i.d. at some point, but the duration and effectiveness of this schedule is not documented. Similarly in study MSD 270, 41 subjects were at one time on 25 mg. q.i.d. again with results that were not well defined. We do not know if they switched to 25 mg. because of toxicity at 50 mg. and then did well or dropped out because of lack of effectiveness. I do not think the existing data is adequate to establish the effectiveness of 25 mg. in OA or RA. There may be sufficient data to permit a note in the labelling that 25 mg. has been found in some patients to be well tolerated and provide adequate relief of symptoms. We should ask the company to organize the available data on the use of 25 mg. in OA and RA, then review that data to see how persuasive it is that 25 mg is the preferred initial dose in these conditions.

In summary, while there is data that at 25 mg ketoprofen is more effective than placebo as a general purpose analgesic, I feel, for the reasons discussed above, that 50 mg is the appropriate initial dose both for general analgesic use and in dysmenorrhea. The label recommendations could say that 25 mg has also been shown to provide analgesia in the range of ASA 650 mg and that 75 mg has been tolerated in some conditions. There is no evidence of the effectiveness of 25 mg in OA and RA and no change in this section of the labelling is appropriate at this time.

Wang #0178J

JS/anta
12-22-86
(See memo in red.)

Palmer
12-30-86

SUMMARY OF KETOPROFEN ANALGESIC STUDIES

Dental Pain

Investig- Keto Control			Plac No.	Results
gator	Dose	Dose		
Cooper	25	ASA	+ 170	Keto 25, 50, 100 mg signif. GT PL. Keto 50, 100 mg signif. GT PL. Keto 25 mg numerically BT ASA
376	50	650		
	100			
Mehlisch	25	Codeine	+ 138	Keto 25, 50, 100 signif. GT PL Keto 25, 50, 100 signif. GT PL Codeine numerically BT PL & signif. GT on recondite summary scores
374	50	90		
	100			
<u>Post Partum</u>				
Sunshine	25	ASA	+ 156	Keto 25 signif GT PL on PI GT (2-3 hrs), PR (2-3 hrs), PID (2-3 hrs) & on summary variables Keto 50 & 100 signif. GT PL (2-5 hrs) & on summary variables Keto 50 & 100 signif. GT ASA on summary scores but not at time points ASA signif. GT PL - at selected timepoints & also on summary variables
375	650			
Kanior	25	Codeine	+ 152	Keto 25, 50 & 100 signif GT PL from 1-6 hrs & on summary variables Codeine signif GT PL at all time points & on summary variables No. significant difference between codeine & Keto
377	50	90		
	100			

SUMMARY OF KETOPROFEN ANALGESIC STUDIES

<u>Dental Pain</u>				ANALGESIC STUDIES	
<u>Investigator</u>	<u>Keto Dose</u>	<u>Control Dose</u>	<u>Plac No.</u>	<u>Subjects</u>	<u>Results</u>
Cooper 376	25 50 100	ASA 650	+	170	Keto 25, 50, 100 mg signif. GT PL. Keto 50, 100 mg signif. GT ASA Keto 25 mg numerically BT ASA
Mehlisch 374	25 50 100	Codeine 90	+	138	Keto 25, 50, 100 signif. GT PL. Keto 25, 50, 100 signif. GT Coi. Codeine numerically BT PL & signif. GT on recondite summary scores
<u>Post Partum</u>					
Sunshine 375	25 50 100	ASA 650	+	156	Keto 25 signif GT PL on PI GT (2-3 hrs), PR (2-3 hrs), PID (2-3 hrs) & on summary variables Keto 50 & 100 signif. GT PL (2-5 hrs) & on summary variables Keto 50 & 100 signif. GT ASA on summary scores but not at time points ASA signif. GT PL - at selected timepoints & also on summary variables
Kantor 377	25 50 100	Codeine 90	+	152	Keto 25, 50 & 100 signif GT PL from 1-6 hrs & on summary variables Codeine signif. GT PL at all time points & on summary variables No significant difference between codeine & Keto

Dysmenorrhea

Lamb 75 IBU. + 36
397-1 400
QID for 3 days
Loading Dose X 2
regular dose

a) First Dose:

Keto signif. GT PL
Ibu signif GT PL
Keto numerically BT Ibu
3 day global:

Keto signif. GT PL
Ibu signif. GT PL

Keto 25 + 75 signif. GT PL
No significant dose response effect but numerical "trends"

Lamb 25 - + 24
349 75
QID for 3 days
3 cycles

Mehlsch 75 IBU + 43
397-II 400
Loading Dose
2X
Regular Dose

a)

First Dose:

Keto signif. GT PL
Ibu signif. GT PL
Keto numerically BT Ibu
3 day analysis

b)

Keto signif. GT PL
Ibu signif. GT PL
Keto numerically BT Ibu.

Post Operative

Sunshine 50 APAP/Cod + 126
398 150/ 650/60

Honig 25 APAP/Cod 74
399 75 650/60

(every 4-6 hrs for 5 days)

Loading Dose Ketoprofen only b)

2X standard

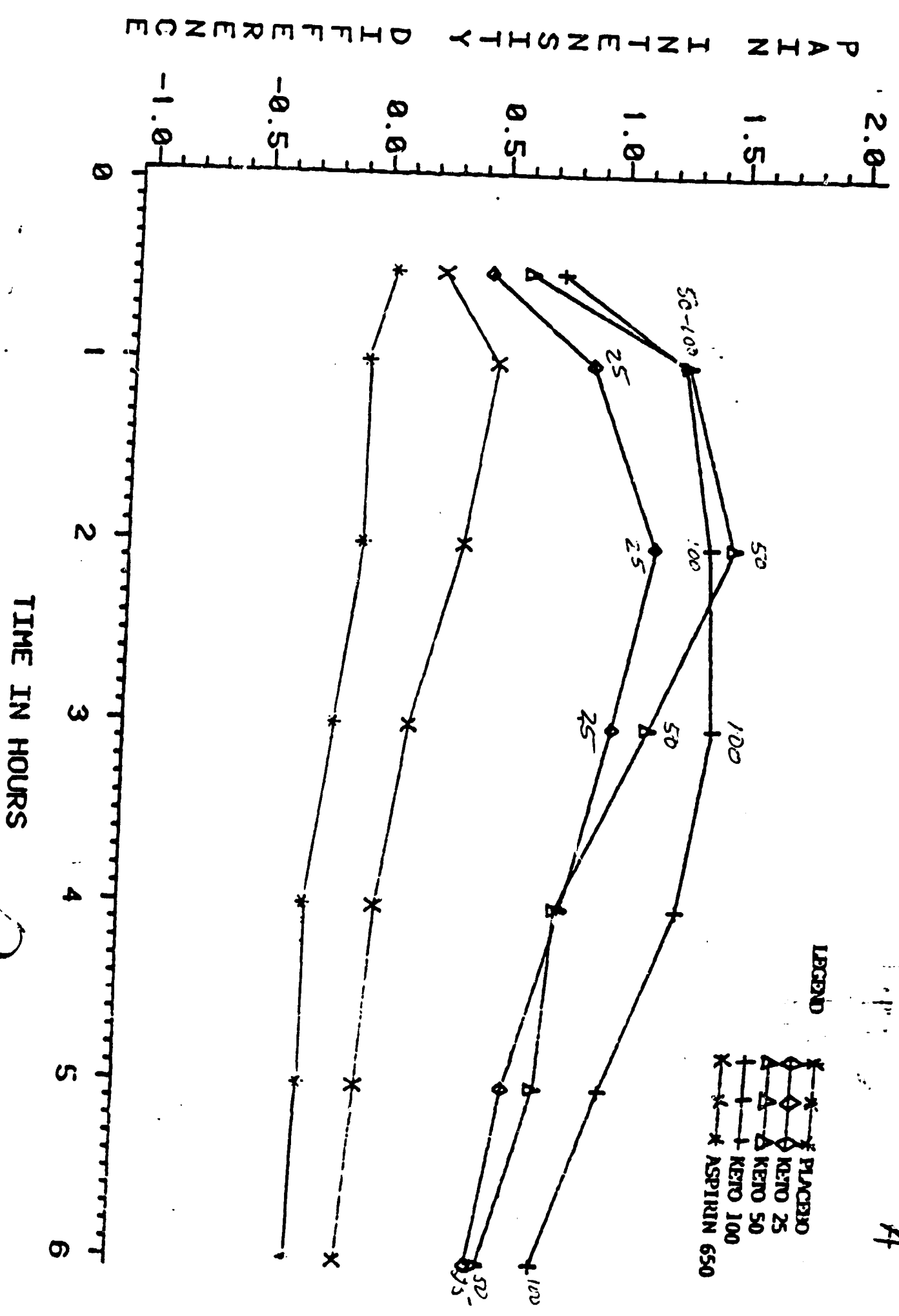
Keto 50 & 150 signif. GT PL (2-6 hrs) & on summary variables

First Dose:

Keto 50 comparable to APAP/Cod
Keto 150 "poorer" effect
No signif. treatment (efficacy) differences
Keto 150 "poorer" effect than
other Rx 2-4 days
APAP/Cod. signif

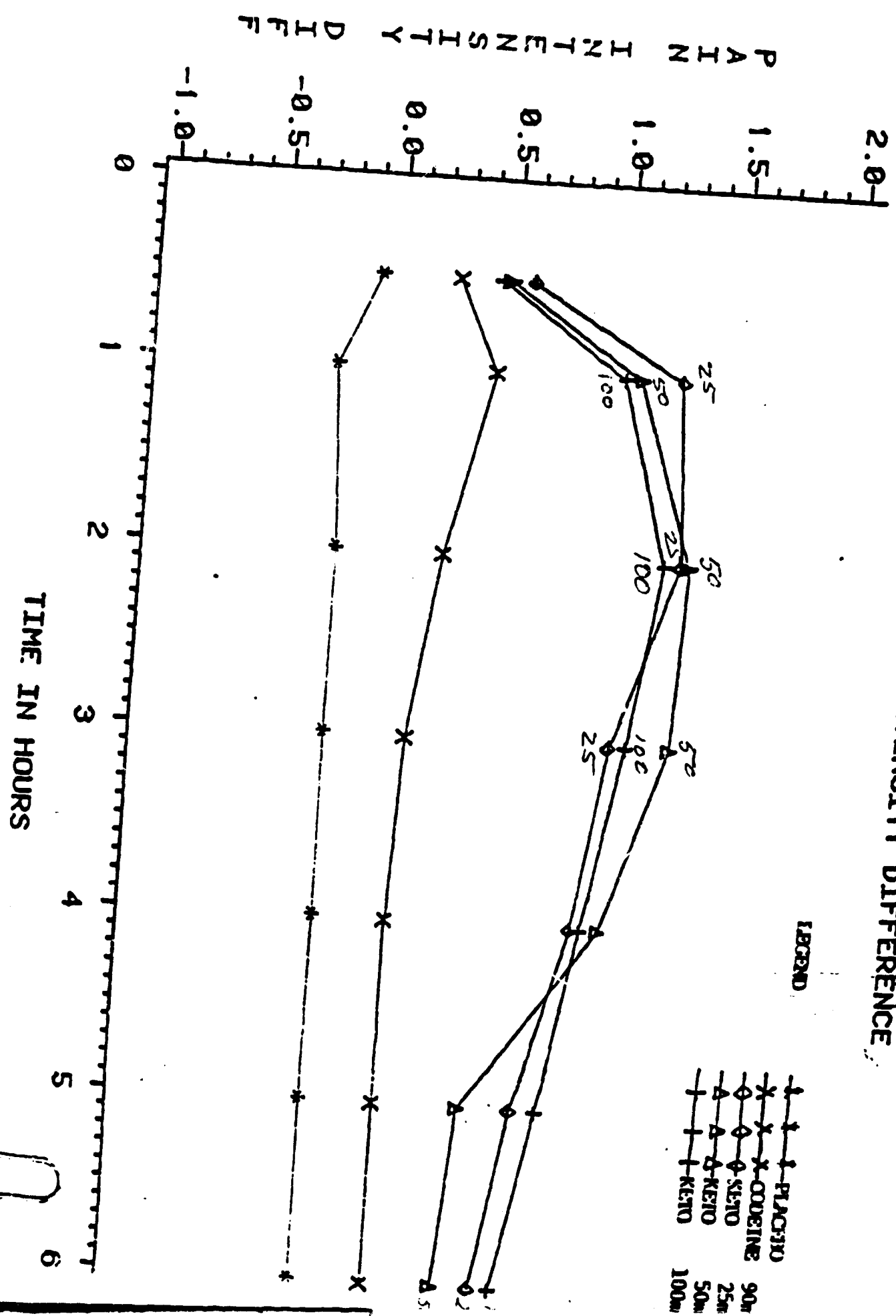
MDS IL 376 - DR. COOPER
 MEAN HOURLY PAIN INTENSITY DIFFERENCES

Mental Pain
 4



Dental Pain

FIGURE 1
 MDS IL 374 DR. MEHLISCH
 MEAN HOURLY PAIN INTENSITY DIFFERENCE



U

FIGURE 1
MDS IL 375 - DR. SUNSHINE
MEAN HOURLY PAIN INTENSITY DIFFERENCES

Post-partum

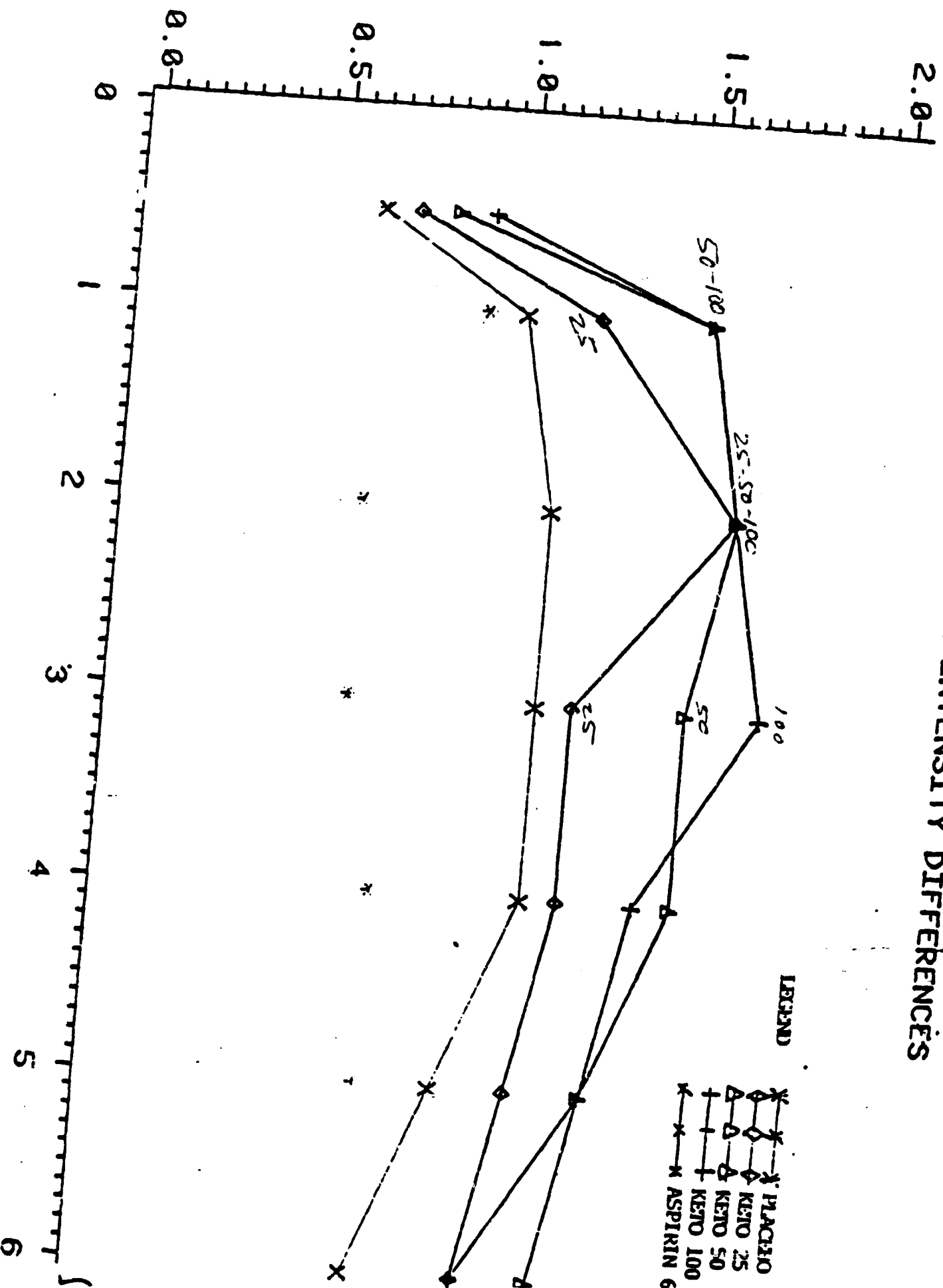
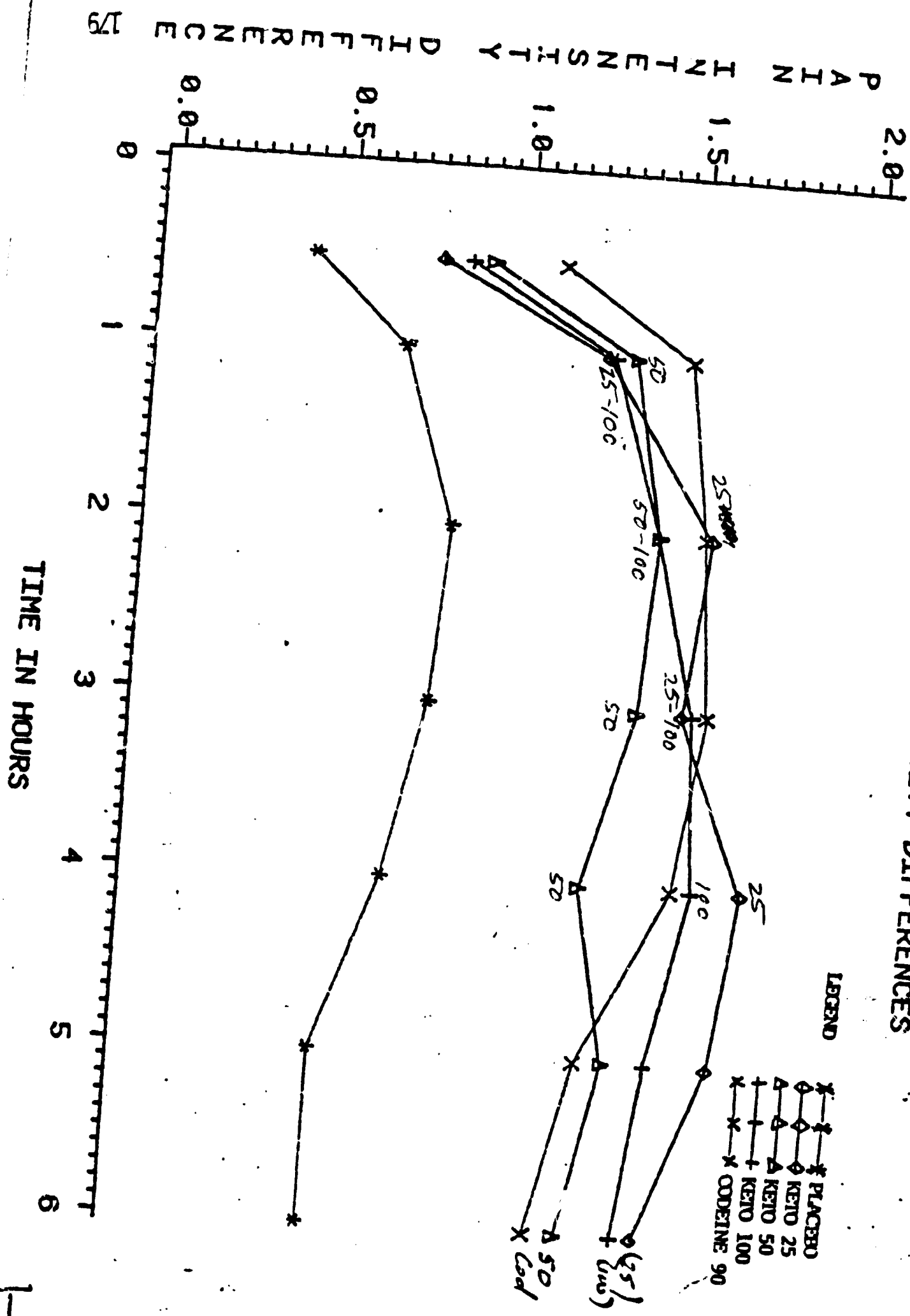


FIGURE 1

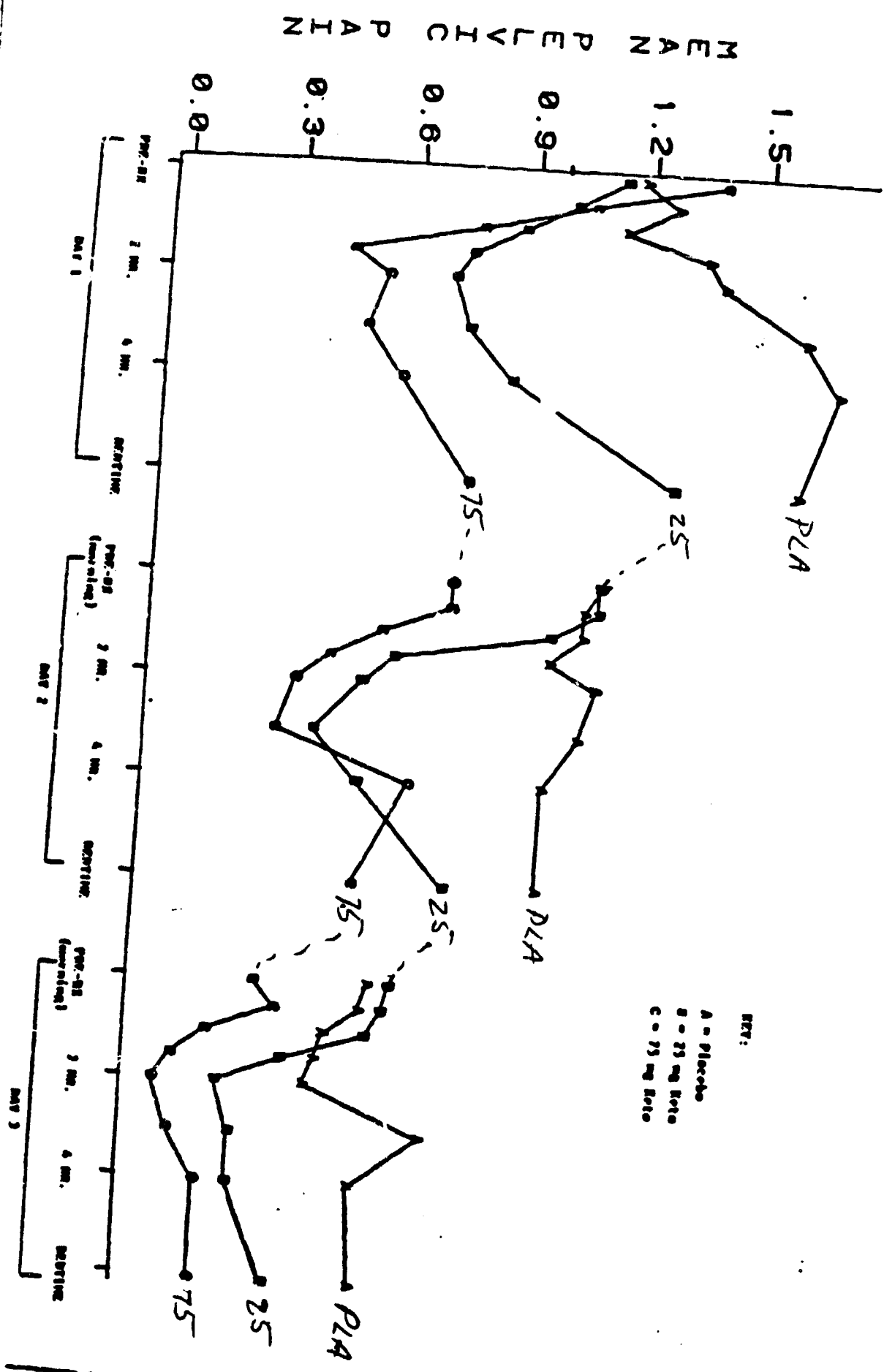
MDS IL 377 - DR. KANTOR
MEAN HOURLY PAIN INTENSITY DIFFERENCES

Post-Partum.



Experiments

FIGURE 11 - Plot of Mean Pelvic Pain Scores

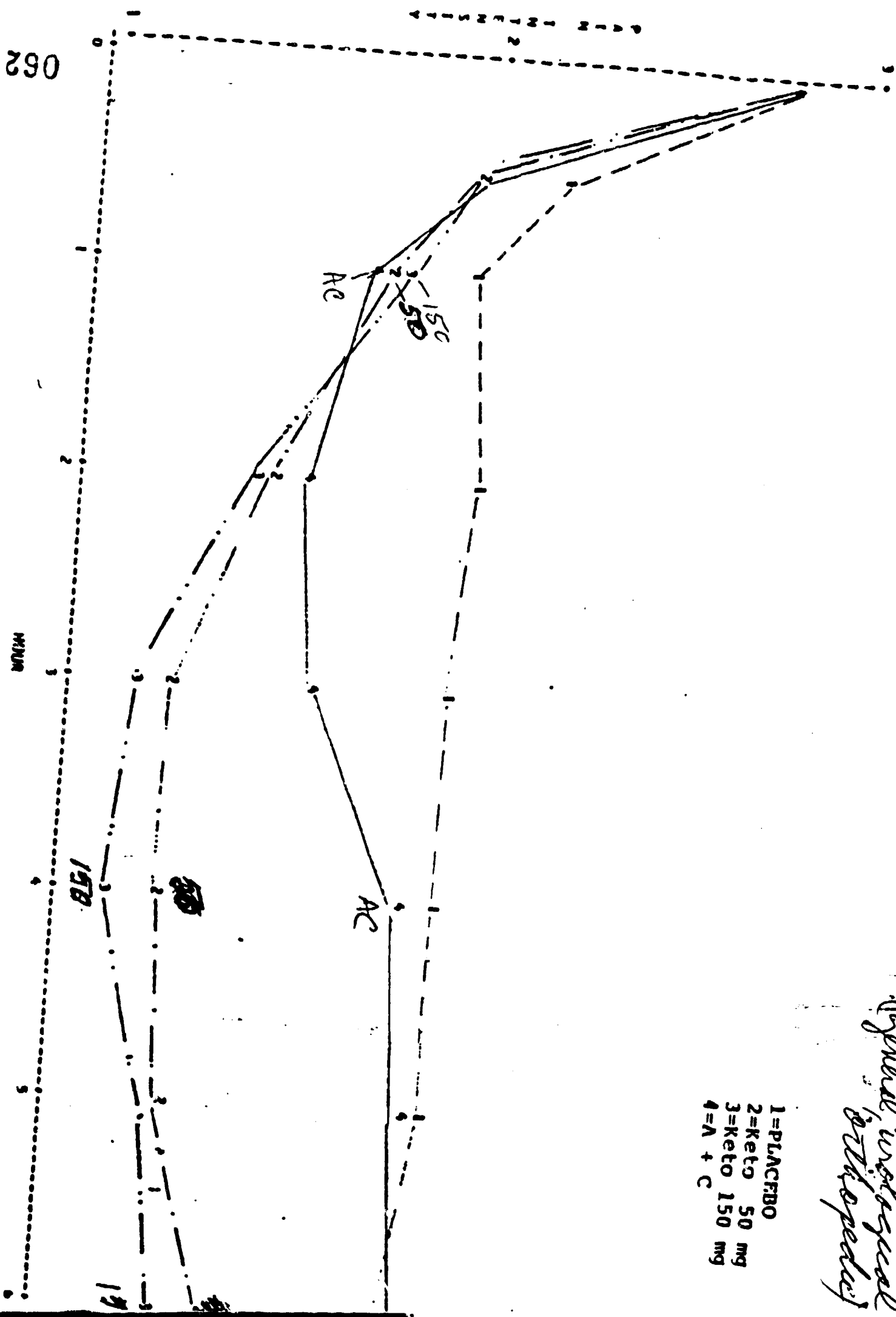


057

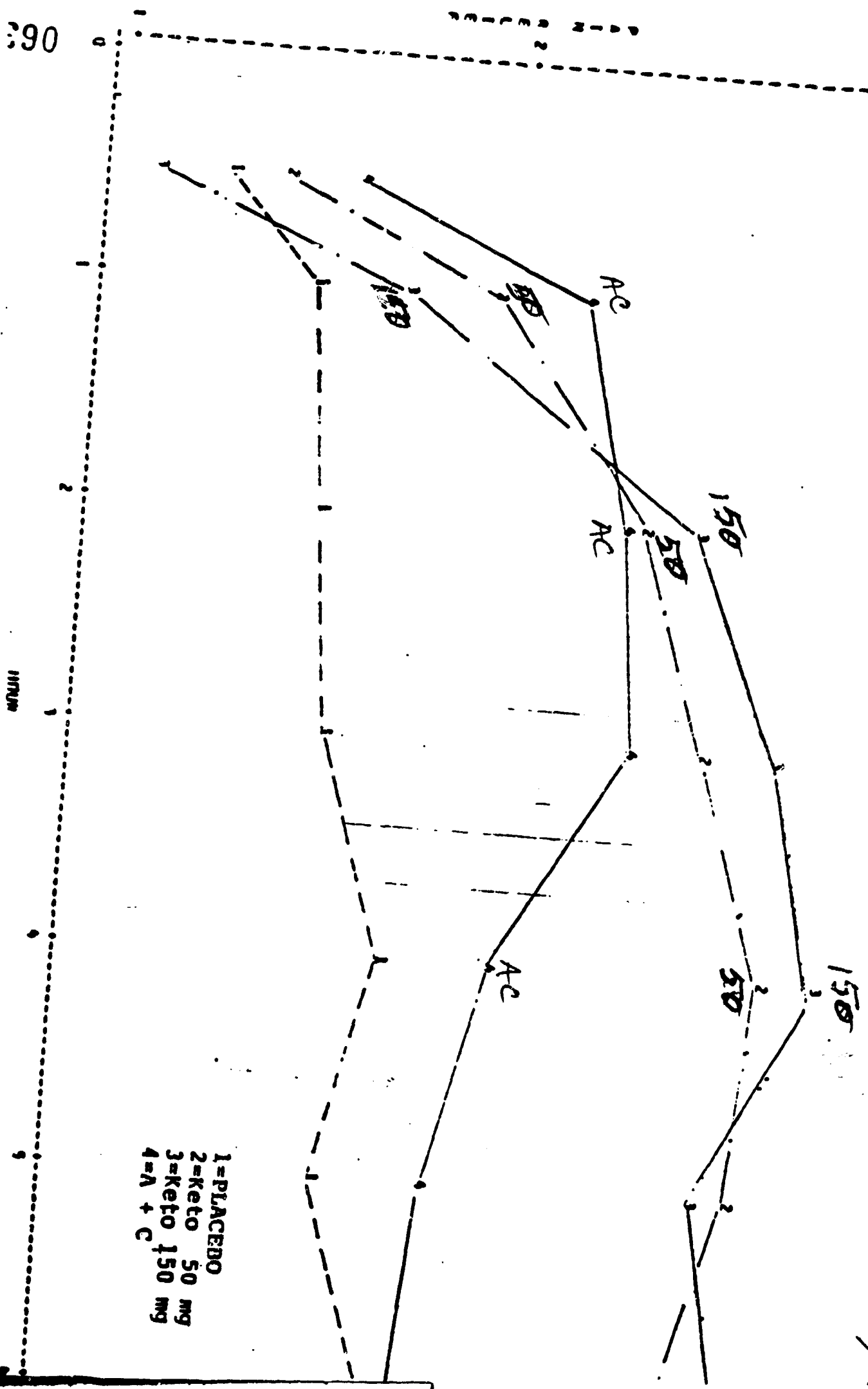
RETORPROGEM STUDY
MPS 198
TIME EFFECT CURVE (PAIN INTENSITY)
FIGURE 1

*Post-op Pain
(General, not specific
to the patient)*

- 1=PLACFBO
- 2=keto 50 mg
- 3=keto 150 mg
- 4=A + C



KETOPROFEN STUDY
 MOS 190
 TIME EFFECT CURVE PAIN RELIEF
 FIGURE 2



Same as
 Ketoprofen
 on octhops

INTENSITY

SEVERE 3.0

MODERATE 2.0

MILD 1.0

0.0

LEGEND: DRUG

HOUR

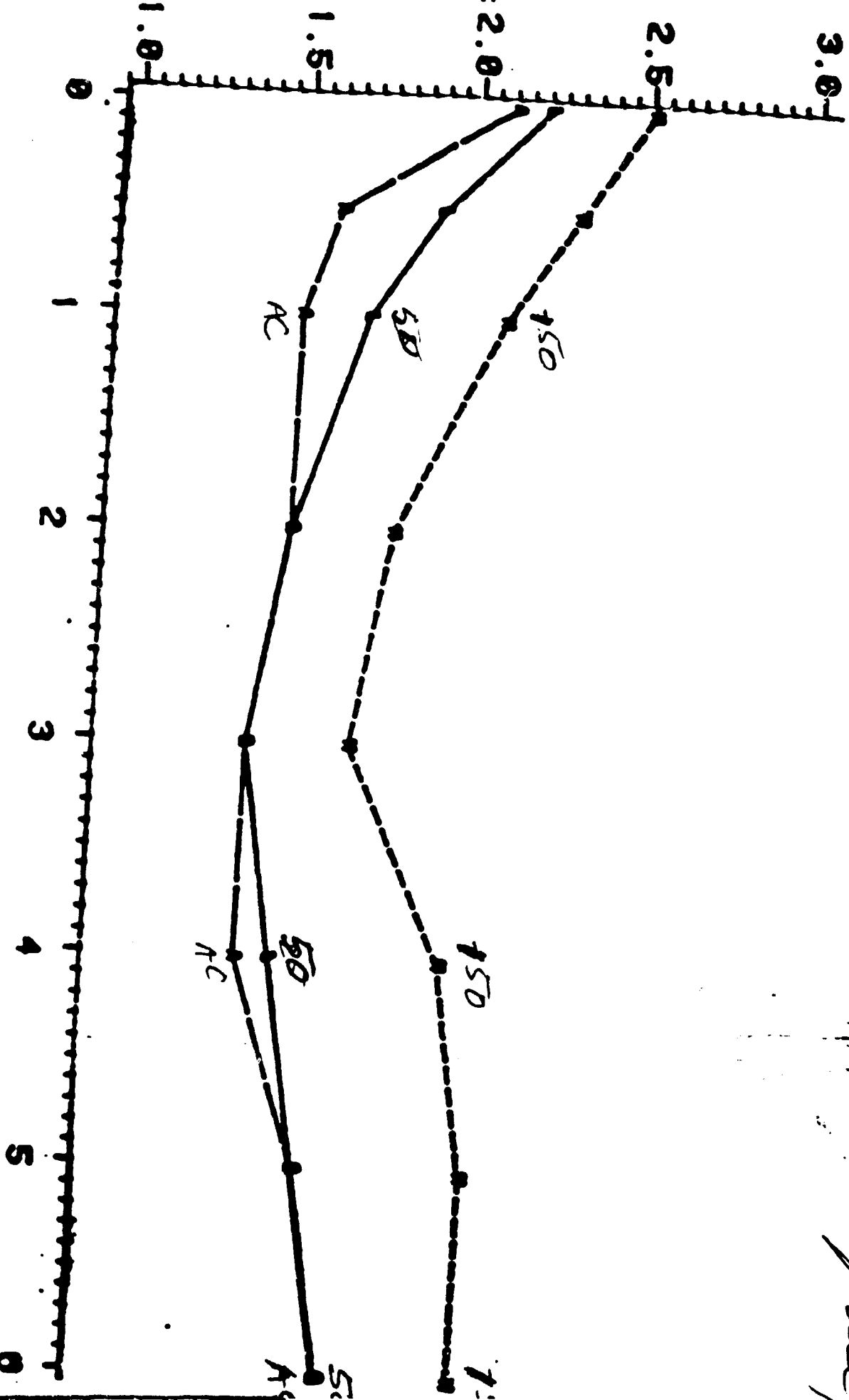
KEIOTROFEN 50 mg
(N=25)
loaded 50 mg

KEIOTROFEN 150 mg
(N=24)
loaded 150 mg

APAP (650 mg)
+CUBKINE (60 mg)
(N=25)
not loaded

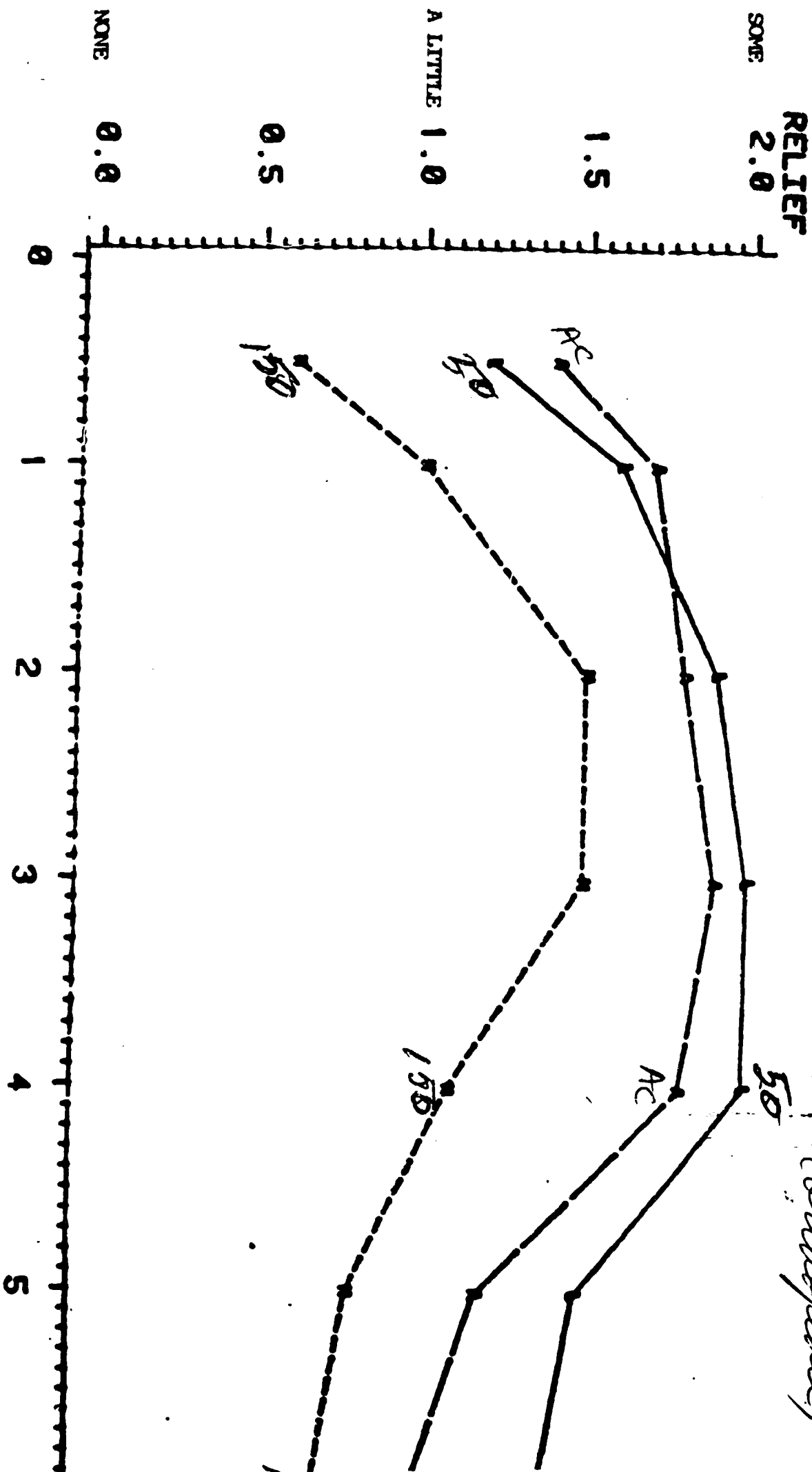
KEIOTROFEN STUDY
M08-199
MEAN VALUES OF SIX-HOUR PAIN INTENSITY SCORE
FIGURE 1

*Peak of pain
with the peak*



KETOPROFEN STUDY
NDS-399
MEAN VALUES OF SIX-HOUR PAIN RELIEF SCORE
FIGURE 2

*Sampled from
(with grade)*



LEGEND: DRUG

HOUR

KETOPROFEN 50 mg

(N=25)

(25 mg group)

KETOPROFEN 150 mg

(N=24)

(75 mg group)

ASPIRIN (650 mg)

+CODEINE (60 mg)

(N=25)

Sampled from

Sampled from

Sampled from

081

Medical Officer's Review of NDA 18-754
Submission of November 1983

Product: ketoprofen (Orduis)

17 Dec 1985

Sponsor: Ives Laboratories
New York, NY

Category: nonsteroidal anti-inflammatory agent

Background

This submission was part of a reply to our letter explaining deficiencies in the initial submission of this NDA. Included in the requested indications for approval is osteoarthritis. Submitted are several clinical studies, including protocol 288AA, dated 12 January 1978.

Protocol 288AA

The study was designed to confirm findings abroad that ketoprofen could relieve the moderate to severe pain of osteoarthritis of the hip or knee. It was a six week double blind placebo controlled study with special emphasis on evaluation of pain relief during week one.

Subjects were to be patients with a diagnosis of OA (clinical and radiologic evidence) requiring regular therapy in the previous three months with aspirin or other NSAIDs. During the two day to two week washout period (salicylate levels tested), evidence of active disease (moderate or severe pain on passive motion with or without restriction of motion, and at night, in the morning or on walking, AND severity of the symptoms moderate in score) had to be obtained. The study was set up as a multicenter study with a projected enrollment of 150.

During the six week drug administration period, ketoprofen was to be administered at either 200 or 300 mg/day qid. No concomitant NSAIDs, or steroids were permitted during the course of the study (a long list of ASA, etc containing products was appended to the protocol). Patients were to be evaluated by serial histories, physical examinations, and laboratory tests including x-rays.

There was a special six hour first dose evaluation. At frequent intervals after dosing subjects were to evaluate the amount of pain, relief, side effects, and overall impression. There was a special first week daily (evening) evaluation of pain using a VAS.

The investigator on a biweekly basis was to evaluate pain on passive motion on a four point scale from no pain to severe pain; restriction of motion on five point scale from no restriction to complete restriction; time to walk 50 feet; and duration of morning stiffness on the morning of the examination. Subjects were to assess the severity of night, morning and walking pain; overall disease activity; and change in condition as compared to entry into the study.

There was an open phase segment of the trial following the double blind segment.

Results

Nine investigators entered 205 subjects. Four were lost to follow up after the baseline visit and are unevaluable. Demographically the randomization procedure appeared to have evenly distributed the subjects. The female to male ratio was 3:1, mean age 66, mean duration of OA of 9 years, mean height of 65 inches, mean body weight of 170 lbs, and 2:1 involvement of knee to hip. Nineteen subjects were dropped from the study for protocol violations including misdiagnosis, use of prohibited medications, failure to take the protocol medication, only one followup visit, etc.

The enrolled 202 subjects were distributed:

300mg/day	200 mg/day	placebo
68	57	58

Of the enrolled 202 subjects, 90 (44.6%) dropped out before the end of the trial (six weeks).

A. Effectiveness

More subjects dropped out of the placebo group for lack of efficacy than from the ketoprofen groups, but the drop out rate reached statistical significance only for the 300 mg/day group ($p = 0.08$). More subjects dropped out of the ketoprofen groups for adverse reactions than the placebo group. The sponsor reports no life threatening adverse reactions which were for the most part related to the gastro-intestinal track. Distribution of drop outs is:

Reason	Number of Patients			Total
	Ketoprofen		Placebo	
	75 mg (N=71)	50 mg (N=64)	(N=67)	
Lack of efficacy	15 (21.1%)	16 (25.0%)	29 (43.3%)	
Intolerable side effect	9 (12.7%)	6 (9.4%)	3 (4.5%)	
Other	3 (4.2%)	5 (7.8%)	4 (6.0%)	
Total	27 (38.0%)	27 (42.2%)	36 (53.7%)	

The mean values for each visit are given in sponsor's Table A.2 (review page 3a). The distribution of subjects between groups appears to be evenly distributed and the subjects appear to have met the entry criteria as to amount of pain they experienced, except for pain on passive motion at 2.3 (2 - mild). Observer and subject assessments of disease activity were 2.2 and 2.3 respectively (2 - moderate). Pain on walking, in the morning, and at night were 3 (moderate).

Mean differences from baseline are given in sponsor's Table A.2.A (review page 3b). The results of the statistical tests of the differences are given in sponsor's Tables A.13 (ANOCOVA) and A.14 (Kruskal-Wallis) (review pages 3c, 3d, 3e). The time points at which statistically significant differences were found in favor of the ketoprofen groups and placebo are summarized by the sponsor:

- (a) Global Assessment (PT) - Week 1 ($p=0.002$)
Week 4 ($p=0.006$)
- (b) Global Assessment (MD) - Week 1 ($p=0.008$)
Week 4 ($p=0.006$)
- (c) Pain on Passive Motion - Week 1 ($p=0.012$)
- (d) Walking Pain - Week 1 ($p<0.001$)
Week 2 ($p=0.008$)
- (e) Morning Pain - Week 1 ($p=0.050$)
Week 2 ($p=0.024$)
- (f) Night Pain - Week 4 ($p=0.015$)
- (g) Duration of Morning Stiffness - Week 6 ($p=0.003$)
- (h) Walking Time - Week 1 ($p=0.002$)

Observer and subject's overall impression on last visit whenever that occurred is tabulated in sponsor's Table A.18 (review page 3f).

B. Toxicity

Principal underlying disease was hypertension in 41% (38% being treated).

Over the course of the experiment, there was a statistically significant weight gain of 1 pound in the ketoprofen group and a loss of 1 pound in the placebo group at all dosing visits. There appeared to be concomitant changes in hemoglobin, hematocrit and plasma protein. There were also increases in BUN (3 mg/dl in the ketoprofen groups), but not in creatinine; and increases in BUN in the placebo group. The sponsor attributes these changes to drug induced changes in prostaglandin synthesis (increases and decreases). There were no statistically significant changes in blood pressure.

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- (d) Walking Pain - Week 1 ($p<0.001$)
Week 2 ($p=0.008$)
- (e) Morning Pain - Week 1 ($p=0.050$)
Week 2 ($p=0.024$)
- (f) Night Pain - Week 4 ($p=0.015$)
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Observer and subject's overall impression on last visit whenever that occurred is tabulated in sponsor's Table A.18 (review page 3f).

B. Toxicity

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Over the course of the experiment, there was a statistically significant weight gain of 1 pound in the ketoprofen group and a loss of 1 pound in the placebo group at all dosing levels. There appeared to be concomitant changes in hemoglobin, hematocrit and plasma protein. There were also increases in BUN (3 mg/dl in the ketoprofen groups), but not in creatinine; and decreases in BUN in the placebo group. The sponsor attributes these changes to drug induced changes in prostaglandin synthesis (increases and decreases). There were no statistically significant changes in blood pressure.

Dr. Robert S. Young
 Rm 9B-45
 Parklawn Bldg.

KETOPROFEN STUDY
 MDS-288AA
 TABLE 1.2
 EFFICACY PARAMETERS
 MEAN VALUES
 ALL INVESTIGATORS

Variable	Treatment	N	Baseline	N	Week 1	N	Week 2	N	Week 4	N	Week 6
Assessment (By Observer) (a)	Ketoprofen (75 mg)	68	2.18	-	-	-	-	-	-	-	-
	Ketoprofen (50 mg)	57	2.18	-	-	-	-	-	-	-	-
	Placebo	58	2.22	-	-	-	-	-	-	-	-
Assessment (By Patient) (a)	Ketoprofen (75 mg)	68	2.37	-	-	-	-	-	-	-	-
	Ketoprofen (50 mg)	57	2.33	-	-	-	-	-	-	-	-
	Placebo	58	2.38	-	-	-	-	-	-	-	-
Pain on Passive Movements	Ketoprofen (75 mg)	68	2.31	67	1.25	58	1.24	52	1.10	41	0.71
	Ketoprofen (50 mg)	57	2.25	56	1.25	46	0.98	40	0.82	34	0.74
	Placebo	58	2.43	55	1.82	37	1.57	37	1.35	28	0.75
Walking Pain (c)	Ketoprofen (75 mg)	68	3.38	67	2.48	58	2.41	51	2.14	41	1.98
	Ketoprofen (50 mg)	57	3.40	56	2.69	46	2.20	40	2.22	34	2.15
	Placebo	58	3.36	55	3.09	37	2.73	36	2.61	28	2.29
Morning Pain (c)	Ketoprofen (75 mg)	68	3.34	67	2.43	58	2.24	51	2.08	41	1.95
	Ketoprofen (50 mg)	57	3.18	55	2.40	46	2.00	40	2.05	34	1.85
	Placebo	58	3.05	55	2.85	37	2.76	36	2.42	28	1.82
Night Pain (c)	Ketoprofen (75 mg)	68	3.04	67	2.07	58	2.03	51	1.83	40	1.75
	Ketoprofen (50 mg)	57	2.89	55	2.20	46	1.91	40	1.88	34	1.79
	Placebo	58	2.98	55	2.45	37	2.41	36	2.28	28	1.82
Walking Time (Sec.)	Ketoprofen (75 mg)	67	20.57	65	17.28	58	17.59	52	18.82	41	17.02
	Ketoprofen (50 mg)	57	22.70	55	20.02	46	17.41	40	16.35	33	16.94
	Placebo	58	19.86	55	21.09	37	20.73	37	19.22	27	14.81
Duration of Morning Stiffness (Hours)	Ketoprofen (75 mg)	68	33.71	66	26.03	58	34.34	52	17.89	40	18.30
	Ketoprofen (50 mg)	57	27.54	55	21.20	46	16.35	40	19.88	34	13.88
	Placebo	58	16.55	55	34.11	38	27.58	36	36.50	28	50.89
Restriction of Motion	Ketoprofen (75 mg)	68	1.47	67	1.17	58	1.09	51	0.82	41	0.73
	Ketoprofen (50 mg)	57	1.48	56	1.07	46	0.96	40	0.85	34	0.76
	Placebo	58	1.67	56	1.79	37	1.14	37	1.16	28	0.93

(d) Restriction Index
 0=none
 1=slight
 2=moderate
 3=almost complete
 4=complete

(e) Pain Index
 1=none
 2=mild
 3=moderate
 4=severe

(f) Passive Motion
 1=none
 2=slight
 3=moderate
 4=severe

KETOPROFEN STUDY

MDS - 288AA

TABLE A.13

EFFICACY PARAMETERS

RESULTS OF ANALYSIS OF COVARIANCE/ANALYSIS OF VARIANCE*

Test the ANOCOVA Model				Analysis of Covariance				
	Week	Covariate	Cov. x Trt.	Joint	Inv.	(Trt.	Inv x Txt.	Joint x Trt.
Global								
	1	-	-	0.619	0.155	0.002	0.669	0.617
	2	-	-	0.059	0.011	0.875	0.668	0.599
	4	-	-	0.225	0.001	0.006	0.254	0.289
by	6	-	-	0.814	0.003	0.207	0.337	0.378
pattern	Last	-	-	0.233	0.090	0.044	0.776	0.748
Global (by covariate)								
	1	-	-	0.449	0.206	0.008	0.791	0.526
	2	-	-	0.008	0.002	0.461	0.794	0.928
	4	-	-	0.158	<0.001	0.006	0.086	0.402
	6	-	-	0.187	<0.001	0.023	0.105	0.880
by	Last	-	-	0.206	0.001	0.034	0.897	0.545
Pain on Motion								
	1	<0.001	0.686	0.302	0.263	0.012	0.344	0.489
	2	0.010	0.310	0.509	0.527	0.295	0.936	0.416
	4	0.054	0.855	0.066	0.302	0.519	0.393	0.922
	6	0.193	0.245	0.778	0.010	0.653	0.163	0.633
	Last	<0.001	0.038	0.957	0.780	0.281	0.893	0.944
Walking Pain								
	1	<0.001	0.564	0.405	0.214	0.001	0.161	0.565
	2	0.020	0.036	0.108	0.178	0.069	0.662	0.760
	4	0.008	0.816	0.121	0.047	0.008	0.479	0.148
	6	0.002	0.684	0.594	0.014	0.655	0.478	0.445
	Last	<0.001	<0.990	0.264	0.407	0.004	0.332	0.868

*Week analysis (i.e., Weeks 1, 2, 4, 6) and for main analysis (i.e., end point analysis at Week 4, indicated by "last" above).

KETOPROFEN STUDY

MDS - 288AA

TABLE A.13

EFFICACY PARAMETERS

SUMMARY OF ANALYSIS OF COVARIANCE*

(Continued)

Test the ANCOVA Model				Analysis of Covariance				
	Week	Covariate	Cov. x Trt.	Joint	Inv.	Trt.	Inv x Trt.	Joint x Trt.
Morning Pain	1	<0.001	0.862	0.791	0.610	0.050	0.568	0.699
	2	0.051	0.351	0.044	0.287	0.024	0.850	0.840
	4	0.007	0.819	0.133	0.208	0.255	0.183	0.933
	6	0.041	0.668	0.817	0.585	0.710	0.504	0.663
	Last	<0.114	<0.808	0.452	0.884	0.129	0.458	0.793
Night Pain	1	<0.001	0.644	0.482	0.436	0.254	0.289	0.357
	2	0.200	0.898	0.015	0.667	0.183	0.759	0.203
	4	0.282	0.468	0.312	0.206	0.015	0.307	0.164
	6	0.039	0.509	0.395	0.519	0.795	0.559	0.675
	Last	<0.018	<0.577	0.309	0.826	0.095	0.662	0.119
Walking Time	1	<0.001	<0.001	0.371	0.075	0.002	0.046	0.065
	2	<0.001	<0.001	0.272	0.690	0.393	0.977	0.242
	4	<0.001	<0.001	0.569	<0.001	0.298	0.955	0.545
	6	<0.001	0.021	0.894	0.070	0.987	0.654	0.909
	Last	<0.001	<0.001	0.693	0.060	0.033	0.435	0.221
Duration of Pain	1	<0.001	<0.001	0.112	0.324	0.612	0.444	0.948
	2	0.003	0.083	0.016	0.210	0.097	0.654	0.035
	4	<0.001	0.024	0.542	0.344	0.055	0.282	0.863
	6	<0.001	<0.001	0.778	0.011	0.003	0.105	0.609
	Last	<0.001	<0.006	0.061	0.194	0.123	0.301	0.079
Restoration of Motion	1	<0.001	0.794	<0.001	0.070	0.664	0.278	0.968
	2	<0.001	0.717	0.002	0.231	0.548	0.281	0.452
	4	<0.001	0.898	0.467	0.037	0.146	0.353	0.472
	6	0.086	0.882	0.215	<0.001	0.687	0.235	0.782
	Last	<0.001	0.804	0.009	0.025	0.118	0.351	0.414

*Week analysis (i.e., Weeks 1, 2, 4, 6) and for main analysis (i.e., end point analysis at Week 4, indicated by "last" above.

KETOPROFEN STUDY

MDS - 288AA

TABLE A.14

EFFICACY PARAMETERS

RESULTS OF KRUSKAL-WALLIS TEST AND
MULTIPLE COMPARISONS FOR TREATMENT EFFECT

Variable	Week 1	Week 2	Week 4	Week 6
~~Global~~ Assessment (Patient)	<0.001*** (H,P) (L,P)	0.276 NS	0.007** (H,P) (L,P)	0.401 NS
Assessment (Observer)	0.003** (H,P) (L,P)	0.104 NS	0.017* (H,P) (L,P)	0.504 NS
~~Pain~~ Active Motion	0.013* (H,P) (L,P)	0.176 NS	0.490NS	0.517NS
~~Walking~~ Pain	<0.001*** (H,P) (L,P)	0.058 NS	0.050* (L,P) (H,P)	0.348 NS
~~Walking~~ Pain	<0.001*** (H,P) (L,P)	0.001*** (H,P) (L,P)	0.147NS	0.783 NS
~~Night~~ Pain	0.036* (H,P)	0.434 NS	0.040* (H,P) (L,P)	0.554 NS
Duration of Morning Stiffness	0.184 NS	0.287 NS	0.051 NS	0.074 NS
Walking Time (30 ft)	0.028* (H,P)	0.100 NS	0.009** (H,P) (L,P)	0.201 NS
Restriction of Motion	0.567 NS	0.783 NS	0.932 NS	0.710 NS

NS = Not Significant
* = Significant at 0.05
** = Significant at 0.01 level
*** = Significant at 0.001 level

(L,P) or (H,P) = Ketoprofen 50mg (L) or
ketoprofen 75mg (H) was significantly
better than placebo (P) based on
result of multiple comparison.

Ketoprofen/Placebo
Osteoarthritis/Analgesic
Multicenter Study
MDS - 288AA

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KETOPROFEN STUDY

MDS - 288AA

TABLE A 18

EFFICACY PARAMETERS
CROSS TABULATION OF TREATMENT AND
OVERALL THERAPEUTIC RESPONSE (OTR)

OTR RATED BY INVESTIGATOR

TREATMENT	MARKED	MOD.	MINIMAL	NONE	WORSE	UNK.	MISS.	TOTALS
Ketoprofen (75 mg)	17	25	12	7	9	1	0	71
Ketoprofen (50 mg)	13	21	9	14	6	1	0	64
Placebo	9	12	9	27	9	1	0	67
TOTALS	39	58	30	48	24	3	0	202

OTR RATED BY PATIENT

TREATMENT	MARKED	MOD.	MINIMAL	NONE	WORSE	UNK.	MISS.	TOTALS
Ketoprofen (75 mg)	17	25	12	7	9	1	0	71
Ketoprofen (50 mg)	13	21	9	14	6	1	0	64
Placebo	9	12	9	27	9	1	0	67
TOTALS	39	58	30	48	24	3	0	202

Occult GI bleeding (positive Hemoccult test) was found in 2% of all tests performed on Ketoprofen subjects (testing was done at each visit), but in none of the placebo subjects. There were no significant differences found between ketoprofen and placebo group for grouped ADR. The most frequent ADR category was upper GI distress (20% - ketoprofen and 13.4% - placebo). The majority of the complaints were diarrhea, constipation, and lower GI distress. Severity was principally mild to moderate. In the open label phase of the protocol, five cases of peptic ulcers developed, with serious bleeding in one.

C. Pain study after initial dosing

The sponsor concluded that inadequate instruction of the investigators in this part of the study resulted in confusion as to what should be done. There were numerous protocol violations and inconsistencies in the reports, e.g. subjects reporting pain as half gone while scoring their pain intensity the same as at baseline; declaring the overall effect as excellent or very good, when pain intensity remained unchanged, became worse or improved by one degree. For the first dose of ketoprofen, NO significant differences could be detected between the effect of placebo and ketoprofen. The sponsor concluded that this part of the trial failed to provide valid data.

DISCUSSION

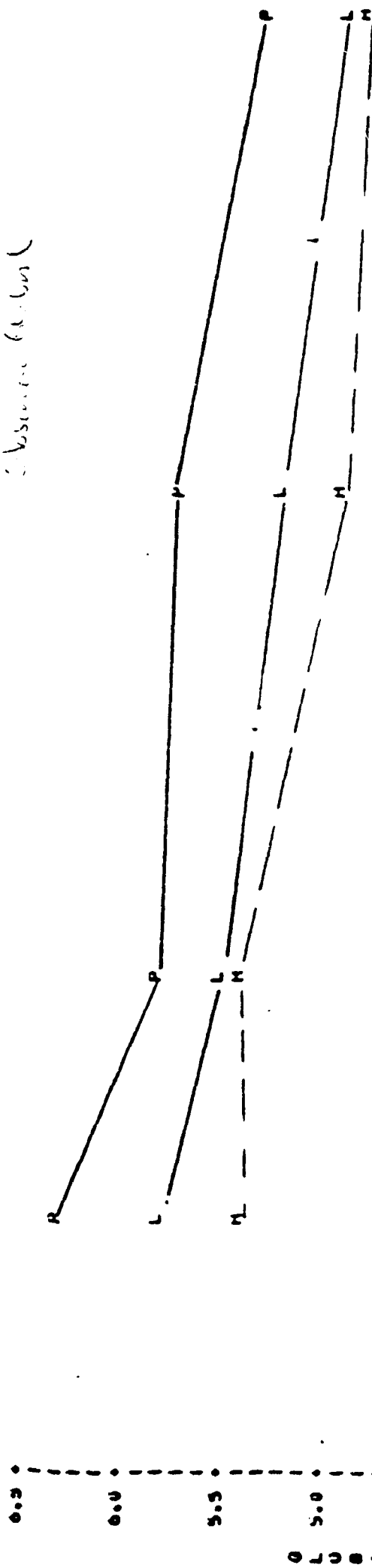
This controlled trial was well designed and except for the special study on analgesic effects in the first week appears to be well executed. The data supports the sponsor's conclusion that the drug provides symptomatic relief for subjects with OA. The drop out rate for lack of efficacy, though not reaching statistical significance at $p = 0.05$ is large enough (twice as many in the placebo group drop out as compared to the experimental group) to be considered therapeutically significant and is reproducible enough ($p = 0.05$) to be acceptable. The drug's drop out rate for adverse effects though larger in the treatment groups than placebo group is sufficiently small so that the drug's therapeutic advantage over placebo is preserved.

Though real and sufficient, the therapeutic effect of this drug appears to be modest, and the study shows a positive effect only through the fourth week. In general all subjects in the study who did not drop out improved during the first to second week of the trial. This is most clearly illustrated in sponsor's charts (see review pages 4a, b, c, d, e). The small differences between groups at six week did not reach statistical significance partly because by then so many subjects had dropped out (most for lack of effectiveness).

Adverse effects appear to be those shared with other members of this pharmacologic group, i.e. renal and gastrointestinal and may be related to their effect on prostaglandin synthesis. The potential of this product to cause GI bleeding after subacute administration should be evaluated in later clinical trials of this drug.

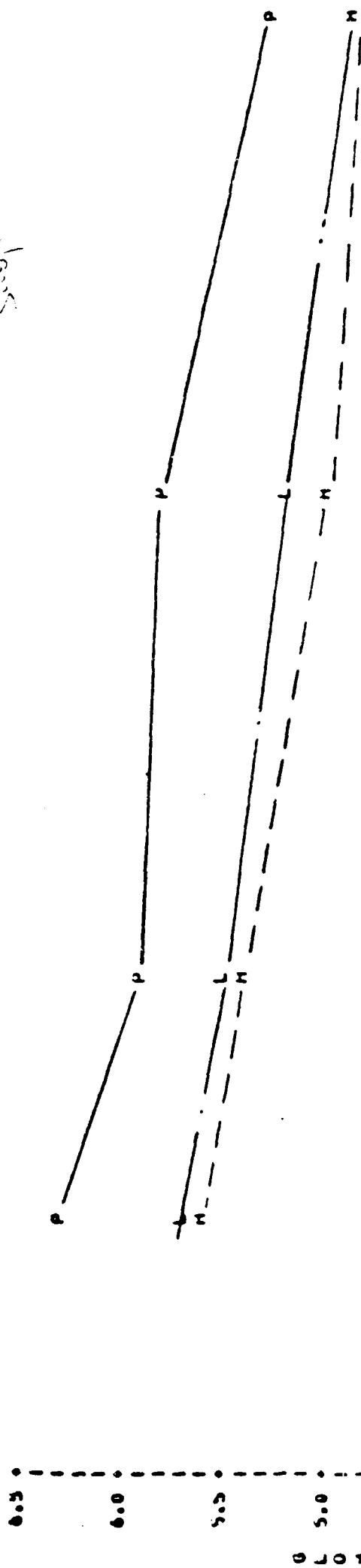
GLOBAL AGREEMENT BY CONSENSUS
ON THE
FUTURE OF THE
MEDITERRANEAN

...bureau (A. L. L.)



P=Placebo
L=Ketoprofen (50mg)
H=Ketoprofen (75mg)

KE TOPROFEN STUDY
MUS
FIGURE 2.A
MEAN DIFFERENCES
ALL INVESTIGATIONS
GLOBAL ASSESSMENT BY PATIENT



Subject (Patient)

P=Placebo
L=Ketoprofen (50mg)
H=Ketoprofen (75mg)

mean

KETOPROFEN STUDY

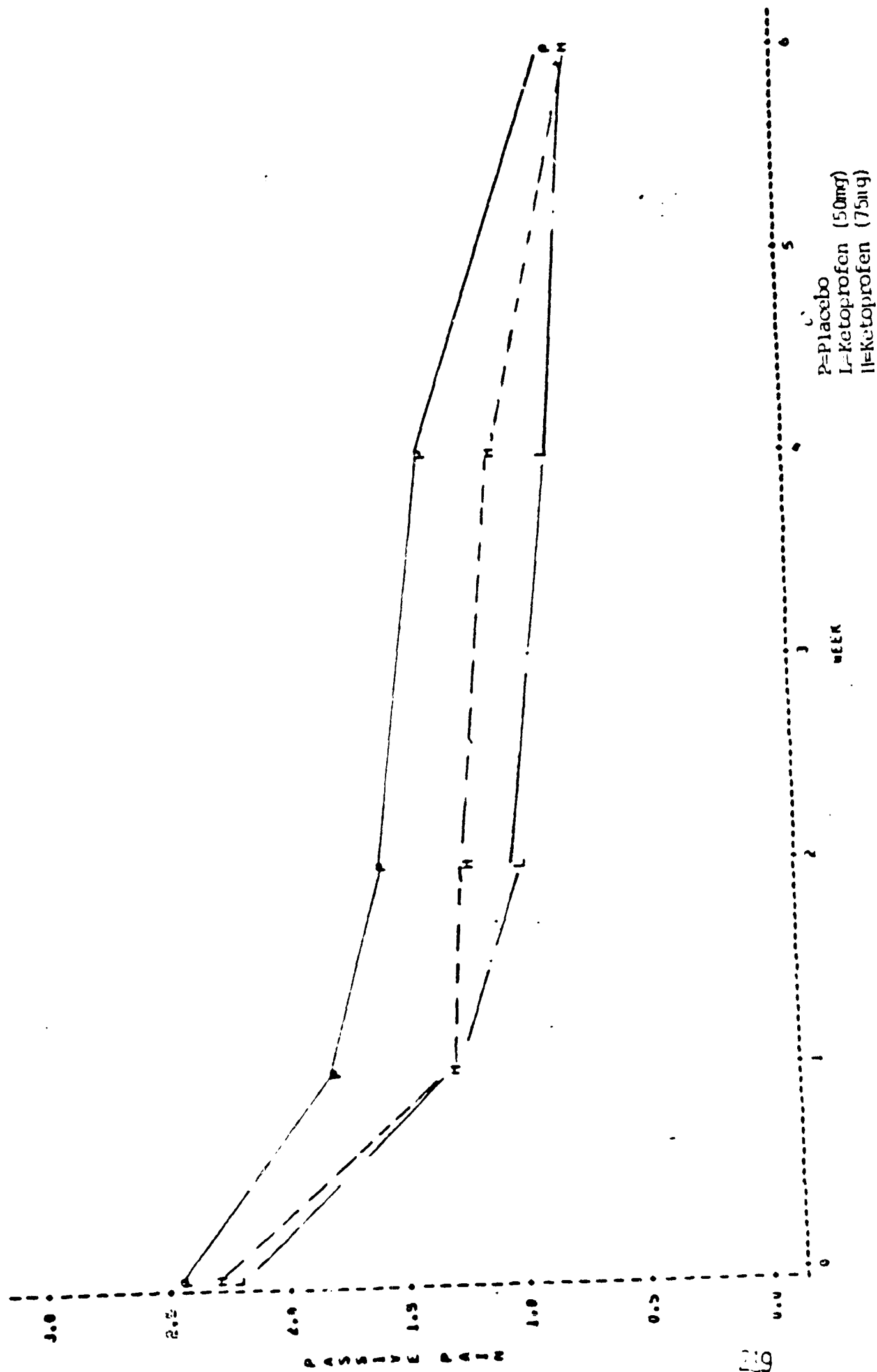
MUS - COBAA

FIGURE 3

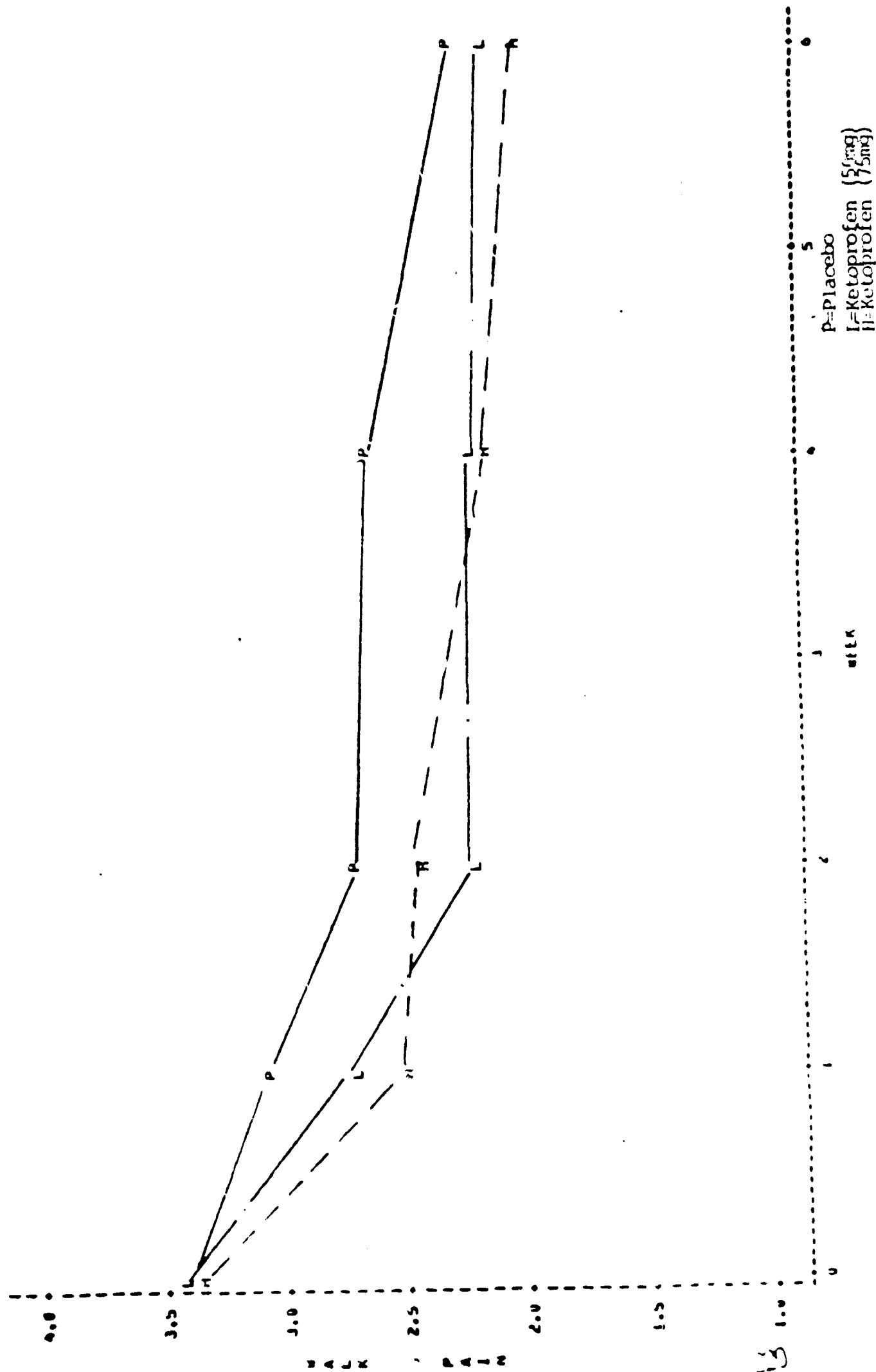
MEAN SCORES

ALL INVESTIGATIONS

PAIN ON PASSIVE MOTIONS

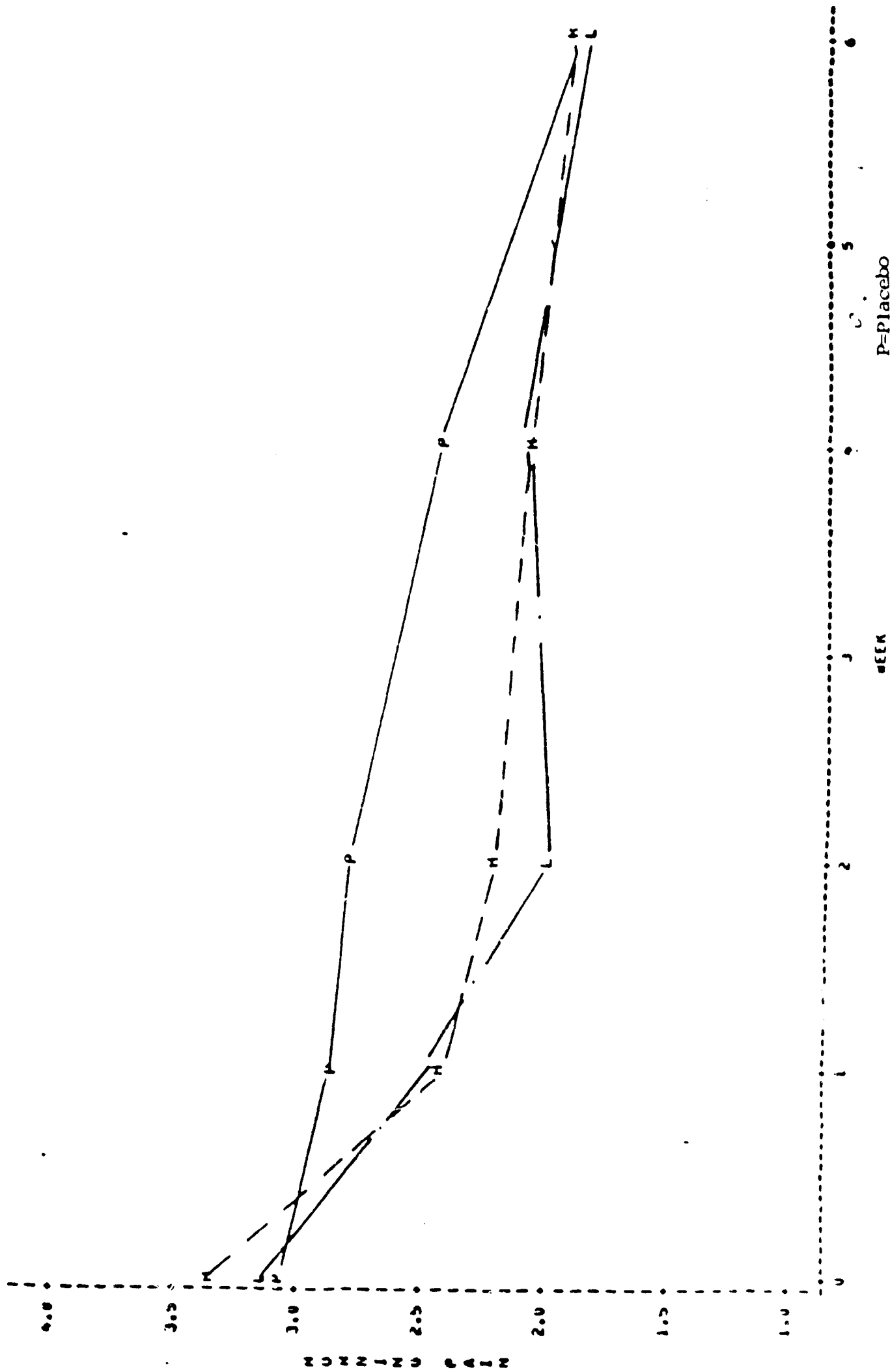


KE TOPHOF STUDY
MUS -2-A
FIGURE 4
MEAN SCORES
ALL INVESTIGATORS
WALKING PAIN



Phase 4-2

2
 RELUPHUS STUDY
 MUS-200AA
 FIGURE 7
 MEAN SCORES
 ALL INVESTIGATIONS
 FORMING PART



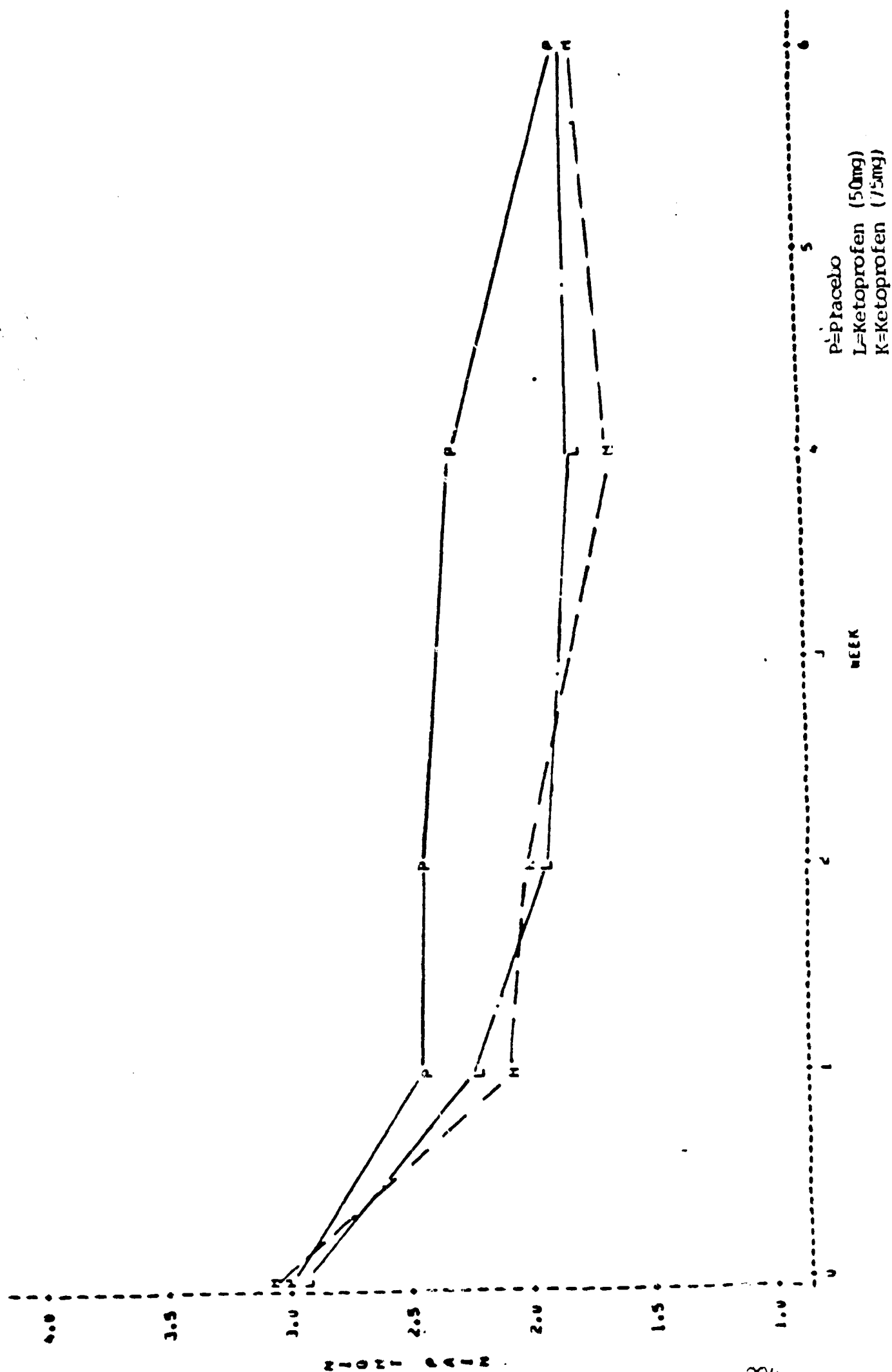
page 42

P=Placebo
 L=Ketoprofen (50mg)

WEEK

2

RETURN STUDY
MUS. DATA
FIGURE 8
MEAN SCORES
ALL INVESTIGATIONS
NIGHT PAIN



Page 4

Although the intensive study of analgesia in the first dosing week failed, such methods should not be abandoned and the sponsor should be encouraged to persist. The results which the sponsor obtained indicate how "soft" some of the usual data obtained really is, i.e. categorical evaluation of pain intensity, overall opinions, etc.

RECOMMENDATION

This study provides substantial evidence of effectiveness in OA as compared to placebo over about four weeks of therapy. The reported adverse effects, which appear to be shared with other members of the group, do not outweigh the drug's therapeutic benefit.

Referring 11/2/85
Robert S. K. Young

NDA 18-745
HFN-150
HFN-150/Pease
HFN-150/Young
Wang 2733B

12-20-85
J. A. Hentrich

DWT

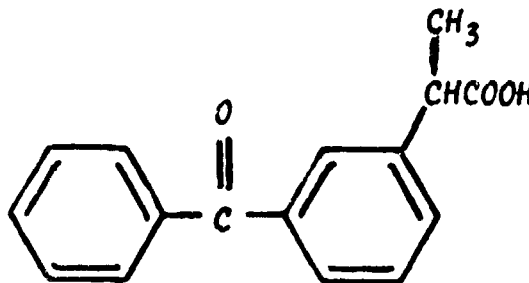
Medical Officer Review of NDA 18-754
Vols. 1.1. thru 738

Original submission dated 3-22-82
Received by me 4-19-82
Reviewed by me 8-19-82

Sponsor: Ives Laboratories, Inc.
685 Third Ave.
New York, NY 10017

I. Description of the Drug Product

- A. USAN: ketoprofen.
- B. Trademark: Orudis.
- C. Therapeutic Claim: Antiphlogistic.
- D. Chemical Name: 2(3-benzoylphenyl)-propionic acid.
- E. Structural Formula:



- F. Molecular Formula: C₁₆ H₁₄ O₃
- G. Molecular Weight: 254.29
- H. Code Designations: IL-19,583;
19-583 R.P.
- I. Mechanism of Action: Unknown, but these antiphlogistics inhibit prostaglandin biosynthesis by interfering with the metabolism of arachidonic acid by inhibiting the enzyme cyclooxygenase which in turn prevents the generation of endoperoxides, thromboxanes, and the prostaglandins PGE₂ and PGF_{2a}.
- J. Metabolism (in monkeys): Plasma levels of orally administered ketoprofen reached a maximum within 1 hour of dosing and subsequently declined with T_{1/2} of approximately one hour and 29 hours.

As in the Beagles, metabolism initially was slight but by the second day water-soluble metabolites accounted for 1/3 to 2/3 of the circulating radioactivity; however, the bulk of the administered dose was excreted in the urine within the first 24 hours and unchanged ketoprofen was by far the major excretion product.

While conjugation products were predominant in man, dogs, and rabbits, hydroxylation products were more abundant in the urine of monkeys and rats. Plasma $T_{1/2}$ in humans is 4 hours.

K. Forms Available: 25, 50, 75, and 100 mg. capsules.

L. Route of Administration: Oral.

M. Dosage: 100 to 300 mg per day in divided doses.

N. Related IND: IND 8891 for ketoprofen, originally submitted 6-28-72 (or sooner?).

II. Chemical Review:

Not yet available.

III. Pharmacological Review:

Not yet available.

III'. Brief Pharmacological Review by the Undersigned:

A. Acute Toxicity

LD₅₀: With the exception of rats, the LD₅₀ of orally administered ketoprofen exceeded 350 mg/kg; adult rats (LD₅₀: 32 to 160 mg/kg) were more sensitive than weanling rats (LD₅₀: 475 mg/kg) and other species.

The age-related difference in acute toxicity can be probably explained by faster metabolism and excretion of ketoprofen in weanling rats.

Ketoprofen was considerably less acutely toxic than indomethacin and displayed toxicity comparable to ibuprofen and naproxen.

Manifestations of acute toxicity varied with the species but in general included sedation, adynamia, diarrhea and emesis (in dogs) on the day of treatment. On subsequent days, the animals exhibited anorexia, diarrhea, and decreased motility. Peritonitis resulting from GI lesions was the major cause of death.

B. Subacute Toxicity

1. 5-day in mice

Ketoprofen (LD₅₀: 180 mg/kg p.o.) was 30 times less toxic than indomethacin (LD₅₀: 5.7 mg/kg p.o.) even when given repeatedly.

2. 5-week and 3-month in dogs

Oral doses ranged from 2 to 36 mg/kg/day in the 5-week study and from 3 to 24 mg/kg/day in the 3-month study. In both studies, dogs receiving the higher doses of ketoprofen developed diarrhea which was sometimes melanic, vomited frequently, became anorexic and consequently lost weight. One animal receiving 24 mg/kg/day died after 12 days of Rx; a pyloric ulcer was found in this dog.

N.B.: Since the toxicity observed in the subacute studies closely paralleled the experience in the chronic 18-month study, except that higher doses were usually required to produce the same changes, only the results of the chronic studies will be presented here.

C. Chronic Toxicity

1. 18-month in rats

4.5, 7.5, and 12.5 mg/kg/day p.o. was administered in the diet to Charles River rats for 18 months. Some animals were sacrificed after 6 months. The majority of both male and female rats receiving the highest dose of ketoprofen died during the study while growth rate among survivors were significantly impaired; these indices were similarly affected in the mid-dose (7.5 mg/kg/day) group, but the changes were not significant. The 4.5 mg/kg/day dose was well tolerated clinically.

Gastrointestinal lesions were common findings among the rats in both the subacute and chronic studies. In the chronic study, ulceration or peritonitis was found in many of the high-dose (12.5 mg/kg/day) group animals dying within the first year. A significant number of rats which survived the full course of treatment (18 months) in the high-dose group, displayed ulceration of the ileum at terminal sacrifice. In other cases, areas of intestinal necrosis, peritoneal adhesions, healed ulcers, or gastric ulceration of varying degrees were found; these lesions were only occasionally found in rats receiving the two lower doses of ketoprofen.

Cystic degeneration of the mesenteric lymph nodes was observed in several animals displaying intestinal lesions and was confined to rats principally in the high-dose group.

The hematology and clinical chemistry variates were consistent with blood loss and infection associated with the GI lesions, particularly in the high dose. Hct, Hb and RBC were depressed, whereas WBC were elevated; the RBC-related variates were depressed only after one year in the mid-dose group but were unaltered at the low dose.

Fecal occult blood was present in animals receiving the two higher doses.

Drug-related renal pathology appeared only in the chronic rat study. Terminally, an increase in kidney weight was noted in treated animals; this change was slight (but significant in the females) in rats receiving the lowest dose (4.5 mg/kg/day). Grossly, the kidneys exhibited cortical scarring, with the incidence increasing at the higher dose. Only rats of the high-dose group displayed any increase in the incidence of microscopic lesions which included dystrophic mineralization and necrosis of the papilla, cross tubular dilation, interstitial fibrosis, and some tubular and glomerular loss in the cortex and medulla. Despite these histopathological lesions, no abnormalities in serum electrolytes or urinary variates were noted.

The ophthalmological examinations were unremarkable.

The incidence of tumors in this study - as well as in the two-year carcinogenicity study - was common to rats of this strain and was equally distributed between the control and drug treatment groups.

2. One-year in baboons

In the chronic study, baboons received 4.5, 9.0, and 27.0 mg/kg/day for one year. One-third of the animals were sacrificed after 6 months and an additional group of baboons receiving indomethacin (4.5 mg/kg/day) was included in this study for comparison.

Results: Only one mortality was recorded in either study (N.B.: in a parallel subacute study, the baboons received 12 or 24 mg/kg/day ketoprofen for 6 weeks or ketoprofen in incremented doses for 10 weeks (6 mg/kg/day for 4 weeks, and 48, 96, and 192 mg/kg/day for consecutive two-week intervals). This occurred in the animal receiving indomethacin for 47 weeks which had a perforated stomach and peritonitis.

Baboons treated with 192 mg/kg/day for 2 weeks displayed a general loss of condition, consumed less food and lost weight. The high-dose-treated baboons in the chronic study also gained less weight during the first six weeks of treatment, but grew well thereafter. In the chronic study, only lesions of the GI tract were clearly associated with the highest dose of ketoprofen; they were relatively mild (small areas of necrosis or congestion in the stomach or intestine) and infrequent, but were apparent after 6 as well as 12 months of treatment. Erosions of the mucosa and punctate hemorrhagic foci were observed in several baboons of the high-dose group of the 6-week study. All animals receiving increasing doses of ketoprofen (consecutively 6, 48, 96, and 192 mg/kg/day p.o.) exhibited ulcers of the pyloric antrum.

Kidney lesions consisting of patchy congestion of the medulla and hemorrhagic and necrotic foci in the papillae were formed only in baboons receiving increasing doses of up to 192 mg/kg/day; no other renal toxicity was observed in the chronic baboon study.

Depressed Hb and RBC counts and the presence of blood pigments and cells in the urine, and occult blood in feces appeared only during the last 2 weeks of increasing ketoprofen (192 mg/kg/day) treatment.

In summary, chronic oral ketoprofen was fairly well tolerated by baboons; only minimal toxicity was observed at doses up to 27 mg/kg/day; higher doses, including 192 mg/kg/day for 2 weeks, produced toxicity similar to that observed in dogs and rats.

D. CARCINOGENICITY STUDIES

1. Mice

Doses of up to 32 mg/kg/d ketoprofen administered in the drinking water did not significantly alter the incidence of tumors occurring spontaneously in this species, nor did it produce any other tumors which would be directly related to treatment.

Spontaneous tumors, including malignant tumors of the lymphoreticular system, hepatomas, and adenomas of the biliary tract, were found with equal frequency in control and treated groups.

By contrast, a two-year treatment with benzpyrene produced epidermoid cancer of the nonglandular part of the stomach, thereby demonstrating the susceptibility of this strain of mice to the effects of known carcinogens.

2. Rats:

Ketoprofen, given at 3.0, 4.5, and 7.0 mg/kg/d in the diet for up to two years, did not significantly alter the occurrence of tumors in any organ system.

Treatment of the high-dose group had to be discontinued after 91 weeks because of high mortality.

The incidences of the most frequently occurring tumors, adenomas of the pituitary, and adenomas and adenocarcinomas of the mammary glands in female rats, were comparable in the ketoprofen and control groups.

E. MUTAGENICITY:

standard in vitro tests failed to demonstrate mutagenic potential of ketoprofen.

F. REPRODUCTION AND FERTILITY

1. Males treated with ketoprofen (3, 6, and 9 mg/kg/d) for 67 days prior to mating proved to be as fertile as untreated controls even at the highest dose, which increased mortality.

The reproductive variates of females mated to these animals, were all WNL.

2. Ketoprofen (3, 6, and 9 mg/kg/d p.o.) was administered to female rats from two weeks prior to mating thru day 14 of gestation at which time the animals were sacrificed. A high incidence of mortality was observed with the highest dose of ketoprofen.

Although there occurred some light but significant alterations in reproduction variates in the mid-dose group with one exception (mean number of implantations), these were not found in the high-dose group, and in both instances the values were very close to the historical controls.

G. TERATOGENICITY STUDIES

1. Rats:

Ketoprofen, administered orally (3, 6, and 9 mg/kg/d) or I.M. (3, 6, and 7.5 mg/kg/d) on days 6 thru 15 of gestation had no impact on maternal or fetal indices of pregnancy.

An increased incidence of maternal deaths was observed at the highest dose by both routes.

The only fetal anomaly discovered was a cranioschisis found in one fetus of an oral high-dose-treated dam; this was considered an incidental finding.

Conclusion: orally or I.M. administered ketoprofen had no embryotoxic effects, no impact on in utero fetal growth, nor any teratogenic effect in rats.

2. Rabbits (NZW):

this strain was extremely sensitive to the toxicity of ketoprofen (2 and 4 mg/kg/d). Maternal weight gain and food consumption were depressed in both treatment groups (significantly only at the high dose). This maternal toxicity probably accounts for the increased number of dead, resorbed fetuses (significant only at the high dose) in this study.

No other reproductive variate was adversely affected by drug treatment.

One abnormal fetus occurred in both the control and high-dose groups.

Although three abnormal fetuses were found in does receiving the low dose, they were all different (double gallbladder, flexed wrists, and a cataract) and had been observed to appear spontaneously in this strain of rabbit. The investigators concluded that the lack of uniformity in fetal abnormalities in this group and the normal incidence of deformities appearing in the high-dose groups were incidental and not drug-related.

I.M. administered ketoprofen (1.5 or 3.0 mg/kg/d) was better tolerated by this strain with no maternal toxicity or embryotoxicity and no abnormal fetuses from any ketoprofen dose.

2.a. Fauve de Bourgogne rabbits (two studies):

Dosage of 3, 6, or 12 mg/kg/d dosage reduction in maternal weight gain and in food consumption were observed at the highest dose in both studies and also at the mid-dose in one.

Some maternal deaths were recorded at both, the high and the mid-doses principally because of GI lesions.

No adverse effects on fertility rates, mean number of implantations, or in utero fetal growth were associated with ketoprofen.

A significant reduction in the average number of live fetuses per litter resulting from increased resorption rates was observed in the mid- and high-dose groups of one study, and in the high-dose group of the other.

This apparent embryotoxic effect was considered as probably secondary to the maternal toxicity produced by ketoprofen at these doses.

II. PERI-NATAL REPRODUCTIVE VARIATES AND POST-NATAL FETAL DEVELOPMENT

1. Mice:

pregnant mice treated on days 5 thru 15 of gestation were allowed to litter normally and the offspring were followed for 30 days after delivery.

The survival indices for and weight gain of pups from treated dams were slightly lower than those from control dams but the difference was not significant. Although ketoprofen was not administered to mice during the period of lactation, the results demonstrate that ketoprofen treatment during pregnancy produced no fetal changes which altered post-natal development and survival.

2. Rats:

A standard Segment III study compared the peri- and post-natal effects of ketoprofen (3, 6, or 9 mg/kg/d p.o.) and indomethacin (1.5, 3.0, or 6.0 mg/kg/d p.o.) in rats; the mortality rates among both high-dose treatment groups were very high. Mortality in the other ketoprofen treatment groups and in the mid-dose indomethacin group was also increased but not significantly above the control group.

Maternal weight gain and the general condition of the animals given the two highest doses of ketoprofen were noticeably inferior to control animals.

There was also delayed parturition in these two groups and in the high-dose indomethacin group (the latter finding is common to NSAIDs).

Because of the poor condition of dams receiving the two highest doses of ketoprofen, meaningful comparisons of post-natal variates could be made only for the low-dose group; in these animals, litter size and pups mortality and weight gain were comparable to the control values; except for a decrease in the number of live births in the mid-dose groups, these same variates were normal in a limited number of animals in the higher-dose groups.

I. PHARMACOLOGY

Ketoprofen was found effective

1. against acute inflammation in carrageenin-induced edema and abscess in rats;
2. against s.c. inflammation in asbestos-and croton oil-induced granuloma in rats;
3. against complex inflammation in adjuvant-induced polyarthritis in rats; in this model ketoprofen inhibited the primary responses as well as the development of the arthritis.
4. ketoprofen antagonized
 - a. paw edema in rats induced by dextran;
 - b. pleurisy in rats induced by intraperitoneal carrageenin and Evans Blue;
 - c. U.V. light-induced erythema in guinea pigs;
 - d. talcum-induced arthritis in pigeons;
 - e. (when applied locally) carrageenin-induced abscesses in rats and urate-induced synovitis in dogs
5. In comparison to other antiphlogistic models, ketoprofen was
 - a. 15 X more potent than ibuprofen;
 - b. equipotent to naproxen;
 - c. 10 to 40 X more active than phenylbutazone.
6. Inhibition of arachidonic acid metabolism:
ketoprofen inhibited the outflow of rabbit-aorta-contracting substance and prostaglandins from perfused guinea pig lungs and in vitro prostaglandin biosynthesis in human lung fragments.
7. Ketoprofen stabilized the lysosomal membranes isolated from the livers of polyarthritic rats.
8. It antagonized the bronchospastic effects of bradykinin in guinea pigs;
ad 6 thru 8: since prostaglandins and bradykinin are mediators of inflammation, and lysosomal enzymes are actively involved in the inflammatory state, the effects of ketoprofen on these processes may all be linked to its antiphlogistic action.

9. In contrast to corticosteroids, ketoprofen did
 - a. not produce thymic involution in rats;
 - b. not aggravate the course of tuberculosis infection in mice.
10. Ketoprofen was equally effective against the carrageenin-induced abscesses in both normal and adrenalectomized rats, thereby suggesting that its mode of action was not thru stimulation of the pituitary-adrenal axis.
11. Ketoprofen displayed marked analgesia in
 - a. peritoneal pain induced in mice by phenylbenzoquinone or bradykinin;
 - b. pain induced by compression of the inflamed paws of rats.
12. In analgesic potency ketoprofen proved to be
 - a. equipotent to indomethacin and naproxen;
 - b. 10X more active than ibuprofen or phenylbutazone (in rats).
13. Similarly to other NSAIDs, ketoprofen was ineffective against pain induced by intraarticular injections of silver nitrate in rats or that produced by pinching the tails of mice.
14. Pronounced antipyretic activity of ketoprofen was noted in the reduction of hyperthermia induced by yeast in rats and antigonococcal vaccine in rabbits; ketoprofen did not alter basal temperature in normal animals. Relative to other NSAIDs incl. indomethacin, naproxen, ibuprofen, and phenylbutazone, ketoprofen was the most potent drug tested.
15. Ketoprofen was a potent inhibitor of platelet aggregation by arachidonic acid and collagen but was very weak when adenosine diphosphate or the combination of serotonin and adrenalin was used.

Administration of ketoprofen to rabbits inhibited for up to 24 hours collagen-induced platelet aggregation.

Ketoprofen also blocked thromboembolic-related death in rabbits produced by the I.V. injection of arachidonic acid.

Despite these effects on platelet function, ketoprofen did not materially alter the coagulation in rats or dogs when administered at pharmacological doses.

16. Similarly to other NSAIDs, ketoprofen produced gastrointestinal lesions in subacute and chronic studies, although less so than indomethacin.

17. The two hydroxylated metabolites of ketoprofen were devoid of antiphlogistic, analgesic, or antipyretic activity when tested at doses up to 100X higher than the pharmacologically effective doses.

J. PHARMACOKINETICS AND METABOLISM

N.B.: for metabolism in monkeys, please see par. I. J. above.

1. Rats

peak plasma levels of orally administered ketoprofen were achieved within 30 minutes, and this was followed by a secondary peak, seen at 2 hours, suggesting of both, gastric and intestinal absorption

Ketoprofen disappeared from the plasma with two T 1/2: 4 to 6 hours and 17.5 hours. The degree of absorption was estimated to be close to 90% upon comparison of the plasma kinetics for the oral and I.V. routes.

By 8 hours, more than 60% of the administered ketoprofen had been excreted and more than 99% had been eliminated after 4 days.

Unchanged ketoprofen accounted for up to 47% of the urinary products, and 22% of the fecal products.

The presence of significant enterohepatic cycling of ketoprofen was demonstrated by the altered excretion pattern in rats with biliary fistulae.

The peak plasma levels of orally administered ketoprofen displayed a direct relationship to dose over the range of 1 to 25 mg/kg. This variate was also unaltered after 5-day pre-treatment with the drug, suggesting that ketoprofen did not induce enzymes for its own catabolism.

The peak plasma concentrations were about 5X lower in weanlings than in adult rats; metabolism and excretion were faster in the young animals but the rate of absorption was not age-dependent.

Up to 87% of ketoprofen was bound to plasma, mainly albumin.

2. Rabbits:

peak plasma levels of orally administered ketoprofen were observed 1 hour after drug administration.

N-18754-5

Ketoprofen and its metabolite, principally a conjugated product, were excreted almost entirely in the urine. Up to 43% of the administered dose was recovered within 2 days with ketoprofen accounting for 14 to 55% of the total.

3. Dogs:

as with rats and rabbits, oral absorption of tritiated ketoprofen by dogs was rapid and almost complete (over 90%). Plasma levels peaked within 1 to 2 hours and then declined with tri-exponential T 1/2: 0.85, 4.3, and 34 hours.

By 8 hours and thereafter, water-soluble metabolites of ketoprofen accounted for more than 50% of the circulating radioactivity.

Approximately 35% was excreted in the urine with unchanged ketoprofen comprising 15 to 32% of the total, mostly in the first 24 hours.

The conjugated metabolite was the major metabolite found in the urine and probably corresponded to the circulating water-soluble metabolite mentioned above.

4 to 5% of the plasma concentrations of ketoprofen were present in milk of the lactating Beagles, and were independent of the time of sampling, thus, the levels of ketoprofen in milk disappeared as rapidly as they did in plasma.

4. Monkeys:

plasma levels of orally administered ketoprofen reached a maximum within 1 hour of dosing and subsequently declined with T 1/2 of approximately 1 hour and 29 hours.

As in the dog, metabolism initially was slight, but by the second day water-soluble metabolites accounted for 1/3 to 2/3 of the circulating activity; however, the bulk of administered dose was excreted in the urine within the first 24 hours and unchanged ketoprofen was by far the major excretion product, thus, the urinary excretion of ketoprofen in monkeys was both significant and rapid and the drug underwent only slight metabolism prior to its removal.

K. TISSUE DISTRIBUTION

In rats, significant amounts of ketoprofen and its metabolites were detected in the stomach, intestine, liver, kidney, and carcass in addition to the plasma; their rates of depletion closely paralleled the decline in plasma levels. No organ displayed a propensity to accumulate either ketoprofen or its metabolites.

The amount of ether-soluble metabolites - which would represent a more lipid-soluble fraction - was minimal relative to ketoprofen and the water-soluble metabolites.

The major metabolites included hydroxylation (on the benzoyl ring) and glucuronides of either ketoprofen or one of the hydroxylation products.

Unchanged ketoprofen was a significant excretory product in all species.

Conjugation was predominant in dogs, rabbits, and r.n., whereas hydroxylation products were more abundant in the urine of rats and monkeys.

IV. HIGHLIGHTS OR CLINICAL STUDIES

A. CLINICAL PHARMACOLOGY

1. Study MDS-280: "Relative Bioavailability of Ketoprofen (Orudis) After Single and Multiple Doses in Normal Volunteers".

Roger L. Williams, M.D., Medical Director, The Drug Studies Unit, San Francisco, CA determined the bioavailability and pharmacokinetics following single-dose administration of three oral formulations containing 50 mg ketoprofen (Orudis, simple capsule without excipients and reference solution) as well as following multiple-dose administration of Orudis (50 mg capsule q. 6 h. for 13 doses) in 12 healthy adult male volunteers; 12/12 completed the single-dose phase, and 6/12 (randomly chosen) the multiple-dose phase. The co-investigators in this study were Sidney Riegelman, Ph.D. and Robert Upton, Ph.D.

Results:

There was no statistically significant difference between the two capsular formations in any of the bioavailability or pharmacokinetic variates.

The peak plasma concentration of the ketoprofen solution was achieved in one-third the time required for the capsules.

Each of the three formulations demonstrated a similar pattern of urinary excretion in that approximately 10% of a 50 mg oral dose of ketoprofen was excreted unchanged (regardless of the formulation) of which 97.9% were recovered in the first 12 hours after drug administration.

The bioavailability from the Orudis capsule relative to that from the solution was $99.7 \pm 10.5\%$ and that from the capsule without excipients was $102 \pm 10\%$.

Plasma concentrations sampled just before the 5th, 9th, and 13th doses indicated that subjects achieved a steady state by the time of the 13th dose.

One case of mild and transient nausea was reported.

In summary, the formulations tested were bioequivalent.

2. Study MDS-330: "Bioavailability of Ketoprofen (Orudis) Following Oral Administration as One 75 mg Capsule and as Three 25 mg Capsules."

Brack A. Bivins, M.D., University of Kentucky Medical Center, Lexington, KY 40506 with coinvestigators Thomas S. Foster, Pharm.D. and Harry B. Kostenbender, Ph.D. determined the bioavailability of (1) 75 mg ketoprofen as three 25 mg capsules in 18 healthy adult male volunteers each of whom received all the three dosages following a one-week interdrug washout.

Results:

The solution formulation showed a faster increase and earlier decrease in plasma concentrations of the drug when compared to either the single 75 mg capsule or the three 25 mg capsules; in agreement with this is the occurrence of a significantly earlier peak plasma concentration when subjects received the solution, s were not achieved.
however, significantly higher peak level

Although a statistically significant difference in the $AUC_0 - \infty$ was observed, the mean difference was slight in magnitude and not clinically significant.

In summary, the three dosage forms are essentially bioequivalent. No clinical ADRs were observed.

3. Study MDS-387: "Relative Bioavailability of Ketoprofen (Orudis) Following oral administration of One 100 mg capsule, two 50 mg capsules, and 100 mg as a Solution."

Brack A. Bivins, M.D., University of Kentucky Medical Center, Lexington KY 40506 with coinvestigator Thomas Foster, Pharm.D. administered (1) one 100 mg Ketoprofen capsule, then (2) two 50 mg ketoprofen capsules, finally (3) 100 mg ketoprofen in solution in an open-label, randomized, three-way crossover design to 12 healthy male volunteers, each of whom received all the three dosages following a one-week interdrug washout.

Results:

The 100 mg capsule and the two 50 mg capsules differed from the 100 mg solution only in their rates of absorption, but not in their extent of absorption. The 100 mg capsule and the two 50 mg capsules were bioequivalent since they did not differ significantly from each other in the rate and extent of absorption. No clinical or laboratory ADRs were encountered.

4. Study MDG-322: "Dose-Ranging Pharmacokinetic and Safety Study of Ketoprofen (Orudis) in Single Oral Doses of 50, 75, 150 and 300 mg."

Brack A. Bivins, M.D., Loc. cit., administered single oral doses of 50, 75, 150, and 300 mg ketoprofen - with one-week washout period between each dose - in an open-label design to 12 healthy adult male volunteers each of whom received all of the four dosages.

The dose-proportionality assessment of the four above mentioned ketoprofen doses was based on the evaluation of plasma and urine levels; area under the plasma concentration-time curve, peak plasma concentration and total urinary excretion were adjusted proportionally so as to correspond to a single dose of 300 mg of ketoprofen, making them equivalent under the hypothesis of pharmacokinetic linearity.

Results:

There were no significant differences among the dose groups in the adjusted rate and extent of absorption. The 75 mg dose group displayed a smaller adjusted $AUC_0 - \infty$ value when the 300 mg dose group was considered as a "reference".

When subjects were administered 50 mg and 75 mg of ketoprofen, greater adjusted mean values of intact ketoprofen recovered from the urine were observed as compared with the 150 mg and 300 mg doses. Analyses of plasma $T_{1/2}$ and plasma clearance also suggested that the disposition of ketoprofen was apparently independent of dose.

In summary, the rate and the extent of absorption, as well as the disposition of ketoprofen, were not dose-dependent for the four dose levels, and it was concluded that the pharmacokinetics of ketoprofen are linear when the drug is orally administered within the range of 50 to 300 mg.

Only 1/12 subject reported mild gastrointestinal upset following the 75 and 150 mg dose, and according to the investigator, this ADR was not directly attributable to ketoprofen.

5. Study MDS-358: "A Study of the Tolerance and Dose Proportionality of Ketoprofen Following Single Doses (50, 100, 150 and 200 mg;" also published as follows:
E. Grundwalt, E. Ruelins and A. Blanstein. Single Dose Tolerance and Pharmacokinetics of Ketoprofen. *Rheumatologie* (Vol.7):105-107, 1973.

Ancel Blaustein, M.D., Booth Memorial Hospital, Flushing, NY administered sequentially single oral doses of ketoprofen: 50 mg on day 1, 100 mg on day 4, 150 mg on day 7, and 200 mg on day 11 to each of ten adult male normal volunteers.

Results:

The dose-response relationship as reflected in the mean ratio of area under the plasma level curves demonstrated that the amount of the drug absorbed was directly proportional to the dose; the estimated $T_{1/2}$ varied from 1.3 to 1.9 hours.

Remarks: Due to certain deficiencies in the design and analysis, the data contained in this study were not used as a basis for any claims concerning dose tolerance or dose proportionality of ketoprofen but were included for completeness.

6. Study MDS-360: "Bioequivalence Study of Ketoprofen Capsules." Mark Bowden, M.D., Drug Evaluation Unit, University of Kentucky Medical Center, Lexington, KY with coinvestigators Thomas S. Foster, Pharm.D. and Harry B. Kostenbender, Ph.D. compared the pharmacokinetics of a single 50-mg capsule of ketoprofen with another identical capsule selected from a different lot in each of twenty adult male volunteers using a randomized, double-masked and crossover design.

Results:

There was no statistically significant difference between the two 50 mg capsules in AUC, plasma levels at each time point, T_{max} and C_{max} , supporting the conclusion that the two 50-mg capsules were bioequivalent. No ADRs were encountered.

7. Study MDS-190: "Effect of Concurrent Administration of Aspirin on Plasma Levels of Ketoprofen following Single and Multiple Oral Doses of both Drugs." Ronald D. Hamilton, M.D., University of Kentucky, Lexington, KY 40506 with coinvestigators Thomas S. Foster, Pharm.D., and Harry B. Kostenbender, Ph.D. administered in a randomized, open-label and crossover design (1) 50 mg ketoprofen of (2) 50 mg ketoprofen and 975 mg aspirin to each of twelve adult male healthy volunteers in the single-dose phase.

Four days after the single-dose phase, the subjects underwent the multiple-dose phase, i.e., they were given the same treatment they had received on the first day of the study, and this dose was repeated at 8-hour intervals over the next three days for a total of ten doses. After a one-week washout, they were crossed over to the other treatment (first the single-dose and after 4 days multiple-dose phase).

Results and conclusion:

The slightly lower C_{max} (3.76 vs. 4.21 mcg/ml) and the slightly delayed t_{max} (86.6 vs. 67.5 min) seen after aspirin administration, may be attributed to a slight and insignificant decrease in absorption rate rather than in any change in volume of distribution or rate of elimination. Possibly, this minor rate alteration might have been caused by the bulk of the three aspirin tablets.

N.B.: Due to the limitations of the assay procedure and the occurrence of high drug level at zero time (2/12 subjects), the results were neither analyzed statistically nor used as a basis for any claims concerning bioavailability.

8. Study MDS-309: "The Effects of Ketoprofen (ORUDIS) on the Anticoagulant Activity of Warfarin."
John D. Arnold, M.D., Quincy Research Center, Kansas City, MO 64127 compared under double-masked conditions the effects of ketoprofen and placebo on the anticoagulant activity of warfarin in 28 healthy adult male volunteers in a 3-phase 22-day study: (1) phase I: single-masked, 12-day warfarin stabilization period; (2) phase II: double-masked parallel 7-day treatment period; (3) phase III: 3-day washout period.

Drug schedule:

Phase I (days 1-12): 7.5 mg warfarin orally before breakfast;
Phase II (days 13-19): randomly, either ketoprofen, 50 mg caps. q.i.d., or placebo caps. q.i.d., in addition to the morning dose (7.5 mg) of warfarin;
Phase III (days 20-22): 3-day drug-free washout.

Results:

This study, conducted to assess the effects of 200 mg of ketoprofen given daily for seven days on the anticoagulant activity of warfarin (7.5 mg/d) in normal adult males, revealed no evidence of a change in mean prothrombin time, i.e., the change was not significant for the whole trial population; however, subjects with an initially high prothrombin time (over 17 sec) had a statistically significant (but not clinically significant) increase of it after the 7-day ketoprofen administration.

ADR: 12 subjects in the ketoprofen-treated group reported 34 ADRs.
12 subjects in the placebo group reported... 49 ADRs.
Most of the ADR were gastrointestinal.

9. Study MDS-318: "An Open Study to Determine the Influence of Concomitant Administration of Ketoprofen (Orudis) on the Therapeutic Activity and Serum Levels of Digoxin in Patients Stabilized on Digoxin Therapy."

George P. Lewis, M.D., Director, Clinical Research Unit, Lemuel Shattuck Hospital, Boston, MA 02113 administered 50 mg ketoprofen q.i.d. for 4 consecutive days to twelve adult patients 3F, 9M, with clinically documented disorder for which digoxin therapy was indicated and who have been stabilized on it for at least one month.

Results:

There were no significant differences among study days with respect to serum digoxin levels (mean values for morning and evening readings on days 1-4 were 0.99 and 1.1 ng/ml, resp., and those on days 5-8 were 0.98 and 1.2 ng/ml).

No change in the ventricular rate or other clinical effects of digoxin was observed.

In summary, concomitant administration of ketoprofen did not alter to any observable degree, the pharmacokinetics or the clinical effects of digoxin.

10. Study MDS-319: "An Open Study to Determine the Influence of Concomitant Administration of Ketoprofen (Orudis) on the Action of Hydrochlorothiazide in Patients Stabilized on Diuretic Therapy."

George P. Lewis, M.D., loc. city., administered 50 mg ketoprofen q.i.d. for 4 days to twelve adult hypertensives, 4F, 8M, stabilized on hydrochlorothiazide.

Results:

Although statistically significant decreases in mean 24-hour potassium and chloride excretion were observed during the concurrent ketoprofen administration, they were not considered clinically significant since they were not reflected by relevant changes in serum electrolytes. Mean serum chloride levels, in contrast, showed a statistically significant ($p = 0.05$) decrease from baseline to follow-up (day 9). In addition, hypokalemia - a common finding with diuretic therapy - was reported in some patients on follow-up (day 9).

Although the body weight decreased, 24-hour urinary volume output and blood pressure remained stable.

In summary, four days of concomitant administration of ketoprofen and hydrochlorothiazide did not clinically alter the diuretic or hypotensive effects of hydrochlorothiazide.

11. Study MDS-323: "A Clinical Study to Assess the Effect of Probenecid on the Pharmacokinetics of ORUDIS (Ketoprofen)."

Roger L. Williams, M.D., Drug Studies Unit University of California, San Francisco, CA 94143 administered in open-label, randomized and two-way crossover design either a 50 mg capsule of ketoprofen q.i.d. alone for 13 doses, or a 50 mg capsule of ketoprofen q.i.d. for 13 doses and a 500 mg tablet of probenecid q.i.d. for 16 doses to each of six healthy adult male volunteers; there was a one-week interdrug washout.

Results: a. Average peak, mean and trough plasma concentrations of total and unbound ketoprofen at steady-state were increased.

b. The overall elimination rate constant (K_{el}) was reduced from 0.66 hr to 0.2 hr.

c. Ketoprofen plasma $T_{1/2}$ was prolonged from 4.0 to 6.6 hours.

d. The total and unbound intrinsic clearance were reduced.

e. The percent of unbound ketoprofen significantly increased from 0.66% to 0.85%.

f. Except of mild GI distress in 2/6 subjects, no clinical or laboratory ADRs were reported.

Conclusions:

probenecid when administered concomitantly with ketoprofen reduced the elimination rate constant of intact ketoprofen, and decreased the total and unbound intrinsic clearances and protein binding of ketoprofen in plasma.

There was no apparent change in the volume of distribution of the central compartment, therefore, the elimination $T_{1/2}$ was prolonged, the total and unbound concentration of ketoprofen in plasma was drastically increased and there was an almost fourfold increase in unbound ketoprofen mean concentrations at steady state.

12. Study MDS-326: "A Clinical Study to Assess the Effects of Aspirin on the Pharmacokinetics of ORUDIS (Ketoprofen)."

Roger L. Williams, M.D., loc. cit., administered either 50 mg capsules of ketoprofen q.i.d. alone for 13 doses, or 50 mg capsule of ketoprofen q.i.d. for 13 doses and 975 mg of aspirin q.i.d. for 16 doses in an open-label, randomized, two-way crossover design to each of six healthy adult male volunteers.

Results: the following variates were demonstrated in the presence of aspirin:

- a. lower ketoprofen ($p = 0.06$) and higher ketoprofen conjugate ($p = 0.22$) concentrations in the plasma;
- b. reduced ketoprofen protein-binding ($p = 0.004$);
- c. decreased elimination of ketoprofen conjugates into the urine after the final dose ($p = 0.004$);
- d. reduction of the peak plasma ketoprofen concentration ($p = 0.029$) but no change in the time to reach this peak drug concentration ($p = 0.7$);
- e. increase in ketoprofen plasma clearance ($p = 0.001$);
- f. the percent of unbound ketoprofen significantly increased from 0.71 to 1.28%, almost 80% more free drug ($p = 0.004$);
- g. when the influence of the decrease in protein binding was eliminated through calculation of clearance based on unbound drug concentration, no significant change in unbound clearance of ketoprofen was noted.

Conclusions:

Aspirin did not alter the amount nor the disposition of unbound ketoprofen.

Since only the unbound drug is presumably pharmacologically active and available to the sites of action, no dosage adjustment would be necessary for ketoprofen when concurrently administered with 975 mg aspirin q.i.d., as far as unbound drug kinetics are concerned.

13. Study 327: "A Clinical Study to Assess the Effect of Orudis (Ketoprofen) on the Pharmacokinetics of Aspirin."
Roger L. Williams, M.D., loc. cit., administered to 9 healthy, adult male volunteers in an open-label, randomized, two-way crossover design either 975 mg aspirin q.i.d. alone for 25 doses, or 975 mg aspirin q.i.d. for 25 doses and a 50 mg capsule of ketoprofen q.i.d. for 32 doses; the first 25 doses of ketoprofen were given concurrently with aspirin; the two treatments were separated by a four-week washout.

Results: there were no statistically significant changes in the kinetics of aspirin for the following variates when given concomitantly with ketoprofen.

- a. average peak, mean and trough plasma concentrations of aspirin at steady-state;
 - b. AUC;
 - c. intrinsic clearance;
 - d. time to peak.
- 2/9 subjects reported mild heartburn and tinnitus, resp.

Conclusions: Ketoprofen did not alter significantly the pharmacokinetics of aspirin in normal subjects.

14. Study 320: "The Effect of Food and Antacid on the Pharmacokinetics of a Single Oral Dose of Ketoprofen (Orudis)." Brack A. Bivins, M.D. and Thomas Foster, Pharm.D., University of Kentucky Medical Center, Lexington KY with coinvestigators Sidney Riegelman, Ph.D. and Robert Upton, Ph.D., The Drug Studies Unit, University of California, San Francisco CA administered in an open-label, three-way crossover design to twelve healthy adult male volunteers either a 50 mg capsule of ketoprofen in a fasting state, or immediately following a standard breakfast, or after 30 ml of Maalox (colloidal suspension of magnesium and aluminum hydroxides).

Results:

- There were no significant differences among the treatment conditions in $AUC_{0-\infty}$, disposition rate constant, plasma $T_{1/2}$ and volume of distribution;
- when ketoprofen was administered after food intake, there was a significant delay in time-to-peak and a lower peak concentration than under the other two treatment conditions;
- there was a significantly higher mean plasma clearance in the non-fasting state;
- there was no significant difference in the cumulative urinary excretion of the drug or in the renal clearance.

Conclusions:

single dose of liquid antacid (30 ml Maalox = magnesium and aluminum hydroxides colloidal suspension) does not alter the rate of absorption or the extent of absorption of a single oral dose of 50 mg of ketoprofen.

When the drug is orally administered immediately after food, the rate of absorption is affected but not the extent of absorption.

B. RHEUMATOID ARTHRITIS - adequate and well-controlled studies:

- Study MDS-306: "A Double-Blind Multicenter Study to Compare the Efficacy and Safety of Ketoprofen with Placebo in Rheumatoid Arthritis"
R. N. Baney, M.D., W. J. Blechman, M.D. F.X. Burch, M.D., W.S. Cryan, M.D., A. J. Cucinotta, M.D., R.M. Fleischmann, M.D., J.W. Griffin, M.D., E. R. Harris, M.D., S.S. Hartman, M.D., E. H. Krick, M.D., B.G. Lanier, M.D., J.S. Spindler, M.D., R.R. Springgate, M.D., and P.D. Vreede, M.D. administered in a randomized, double-masked and parallel design for 6 weeks to 284 patients with adult-onset of definite or classical R.A., 212F, 72M, age 21-77, mean 51.4 years, with the mean duration of R.A. of 7.2 years, stage 1 68/284, stage 2 153/284 stage 3 60/284, stage 4, 3/284, (functional) class mean 2.15, 52/284 with previous chrysotherapy, the following three drug products:

- a. ketoprofen, 50 mg q.i.d. (97/284 pts.);
- b. ketoprofen, 75 mg q.i.d. (93/284 pts.); and
- c. placebo, q.i.d. (94/284 pts.). An up to 2 weeks washout preceded the drug administration. The patients were evaluated at baseline and at (six) weekly intervals thereafter.

Analgesics and other antiphlogistics were not permitted except for acetaminophen which was to be dispensed by the investigator as a rescue drug (during the first week of double-masked therapy only).

Weekly urine ferric chloride tests were to be performed as a compliance assessment in order to establish the patients' non-use of products containing salicylates.

Concurrent medications for illnesses unrelated to R.A. but which coexisted with it at baseline were permitted throughout the study as well as intercurrent medications for illnesses occurring during the study that had not been present at baseline.

Dropouts: 22/284 with 15/22 for dosage violations 2/2 wrong diagnosis, 2/22 concomitant medication, 3/22 too brief Rx period.

Comparability at baseline:

no significant intergroup differences were detected in vital statistics, diagnostic classification, use of chrysotherapy, severity of patients' symptoms as expressed in their ratings of the twelve efficacy variates.

Significant interactions between treatment and investigator were seen in 2/12 variates (walking time and global assessment by investigator) but they did not preclude the analysis of the pooled populations.

1.1. Efficacy

- 1.1.1. The following four efficacy variates were analyzed at the last visit for the percentages of patients improved per treatment group:

	<u>Ketoprofen 200 mg/d</u>	<u>Ketoprofen 300 m/d</u>	<u>placebo</u>
a. <u>investigator's global evaluation:</u>	58.4%	47.7%	42.4%
b. <u>patient's global evaluation:</u>	62.5%	50.6%	42.4%
c. <u>morning stiffness duration:</u>	58.4%	59.1%	37.6%
d. <u>grip strength:</u>	49.4%	51.1%	30.4%

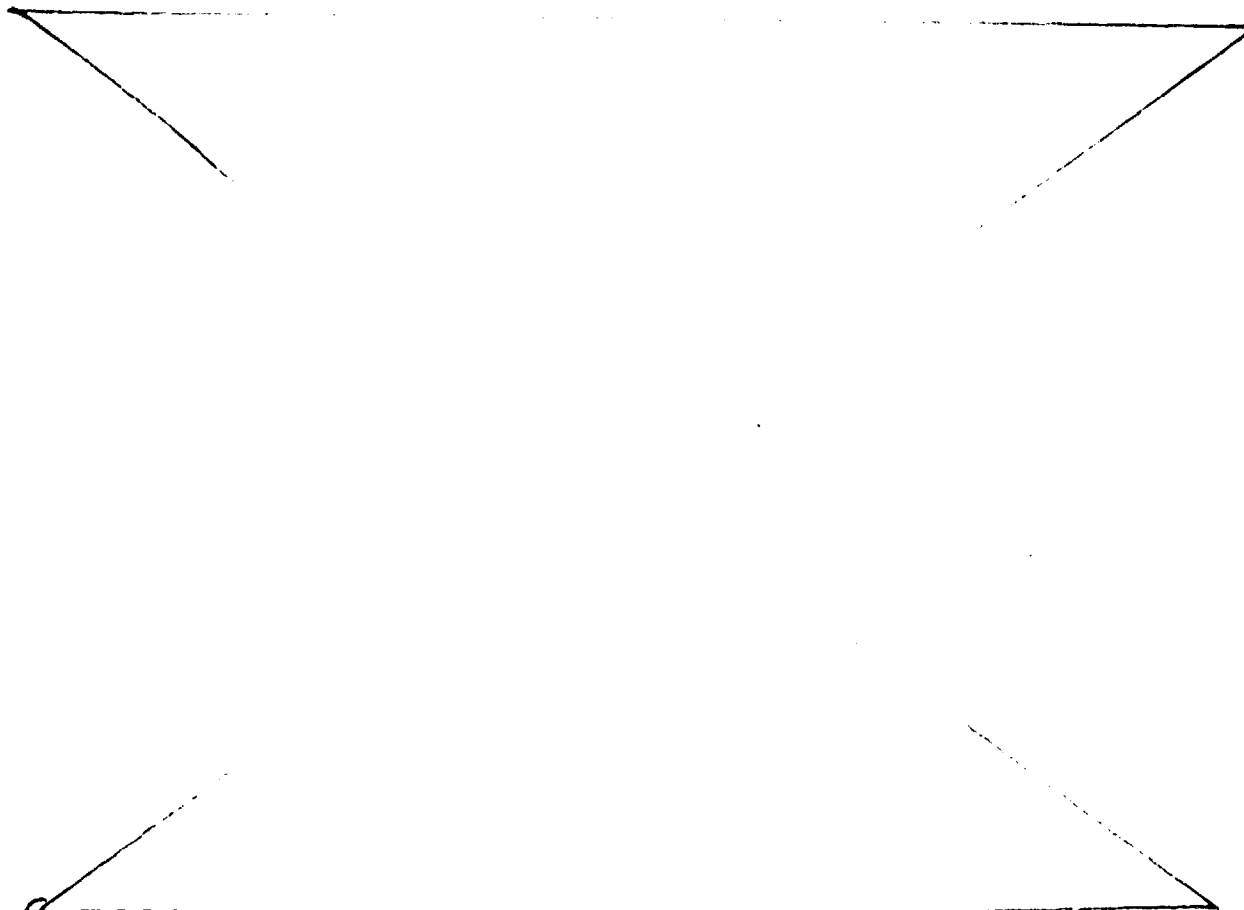
Evaluation:

both ketoprofen dosages statistically significantly superior over placebo in investigator's and patient's global assessments ($p < 0.01$) and in morning stiffness duration ($p = 0.001$) and of borderline significance ($p = 0.087$) for grip strength.

N.B.: grip strength has been documented by me previously as not a powerful discriminatory variate (L.O.).

1.1.2. Mean change from baseline to the last visit

	<u>Ketoprofen 200m/d</u>	<u>Ketoprofen 300m/d</u>	<u>placebo</u>
a. <u>walking time:</u>	-2.2	-4.2	-0.7
<u>Evaluation:</u>	ketoprofen 300 m/d borderline superior at p 0.1 to ketoprofen 200 mg/d and placebo;		
b. <u>functional class:</u>	-0.17	-0.16	-0.06
<u>Evaluation:</u>	no statist. significant intergroup differences;		
c. <u>grip strength:</u>	+19	+18	+8
<u>Evaluation:</u>	both ketoprofen dosages superior to placebo at p 0.05;		



- d. morning stiffness
(hr): -3.0 -3.0 -0.5
Evaluation: both ketoprofen dosages superior to placebo at p 0.001;
- e. investigator's
global assessment -0.62 -0.63 -0.44
Evaluation: no statistically significant intergroup differences in this, usually most powerful, variate;
- f. patients global
assessment: -0.66 -0.68 -0.32
Evaluation: both ketoprofen dosages superior to placebo at p 0.05;
- g. investigator's
global
comparison +2.33 +2.44 +2.81
Evaluation: ketoprofen 200 mg/d superior to ketoprofen 300 mg/d and placebo at p <0.01;
- h. patients' global
comparison: +2.34 +2.51 +2.91
Evaluation: ketoprofen 200 mg/d superior to ketoprofen 300 mg/d and placebo at p 0.01;
- i. joint tenderness
total severe -18.1 -12.7 -10.2
Evaluation: ketoprofen 200 mg/d borderline (p <0.1) superior to ketoprofen 300 mg/d and placebo;
- j. joint tenderness,
total number: 9.1 -8.3 -6.0
Evaluation: intergroup differences N.S.;
- k. joint tenderness
of mod. &
severe -6.4 -3.7 -3.8
Evaluation: same as in par. i. above.
- l. joint swelling,
total score: 9.7 -8.4 -7.5
Evaluation: intergroup differences N.S.;
- m. joint swelling,
total number: -5.4 -4.7 -4.2;
Evaluation: intergroup differences N.S.;
- n. joint swelling,
mod. &
severe: -3.4 -2.7 -2.7;
Evaluation: intergroup differences N.S.

1.1.2.1 Conclusions:

- a. Out of 14 variates, only in 3/14 were both ketoprofen dosages superior to placebo: grip strength and global assessment by the patient, both at $p < 0.05$ and in morning stiffness duration ($p < 0.001$);
- b. Only the 200 mg/d ketoprofen dosage was superior to placebo (and to ketoprofen 300 mg/d) in additional 2/14 variates at $p < 0.01$: global comparison by investigator and by patient;
- c. similarly, only the 200 mg/d ketoprofen dosage reached borderline superiority ($p < 0.1$) over placebo, and over 300 mg/d ketoprofen dosage;
- d. in 1/14 variates, ketoprofen 300 mg/d was superior to placebo (walking time) at borderline significance ($p < 0.1$); there was no significant difference between ketoprofen 200 mg/d and placebo for this variate;
- e. in the remaining 6/14 variates, there were no significant intergroup differences.

1.1.2.2 Summary:

In only 3/14 variates was there any superiority of both ketoprofen dosage over placebo. In only 2/14 variates was there any statistically significant superiority of 200 mg/d ketoprofen (but not of 300 mg/d ketoprofen !) dosage over placebo.

In the remaining 9/14 variates, there were either borderline significant (3/9) or no significant intergroup differences (6/9 variates).

1.1.3. Week 1 - therapeutic responses - statistical significance between ketoprofen and placebo

- a. 50-feet walking time: $p = 0.03$ (300 mg)
- b. functional class: N.S. (0.18)
- c. mean grip strength: < 0.001 (200 and 300mg)
- d. morning stiffness duration: do.
- e. investigator global assess.: 0.001 (200 and 300 mg)
- f. patient global assessment: do.
- g. investigator comparison: do.
- h. patient comparison to baseline do.
- i. tender joint index: 0.002 do.
- j. #mod. or severe tender joints: 0.012 (200 mg only)

- k. ~~# min.~~ mod. sev. tender joints: 0.008 (200 and 300 mg)
- l. swollen joint index: 0.03 (300 mg only)
- m. # mod. or sev. swollen joints: 0.029 (200 mg only)
- n. # min., mod. or sev. sw. joints: N.S.

1.1.3.1 Conclusions

- a. Out of 14 variates, 8/14 improved statistically significantly over placebo in both ketoprofen groups at week 1;
- b. in addition, 4/14 variates improved significantly either in the 200 mg/d group (2/4) or in the 300 mg/d group (2/4).
- c. 2/14 variates did not improved significantly as compared to placebo at week 1.

1.1.3.2 Summary:

satisfactory improvement was observed in most variates, in both ketoprofen groups when compared to placebo after one week of treatment.

1.1.4. Mean changes from baseline to the average visit
ketoprofen 200 mg/d vs. ketoprofen 300 mg/d vs. placebo

- a. 50-feet walking time: -1.9 vs. - 4.2 vs. - 1.0
Evaluation: ketoprofen, 300 mg/d, superior to placebo and to ketoprofen, 200 mg/d at $p < 0.05$;
- b. functional class: -0.17 vs. - 0.15 vs. -0.07
Evaluation: N.S.;
- c. grip strength: +21 vs. + 20 vs. +6
Evaluation: both ketoprofen dosages superior to placebo at $p < 0.001$;
- d. morning stiffness dur.: -3.0 vs. - 3.1 vs. -0.5
Evaluation: both ketoprofen dosages superior to placebo at $p < 0.001$;
- e. inv. global assessment: - 0.72, vs. - 0.73 vs. - 0.44
Evaluation: both ketoprofen dosages superior to placebo at $p < 0.05$;
- f. pt.'s global assessment: -0.77 vs. - 0.8 vs. - 0.36
Evaluation: both ketoprofen dosages superior to placebo at $p < 0.01$;

- g. inv. global comparisons: +2.19 vs. +2.32 vs. +2.75
Evaluation: both ketoprofen dosage superior to placebo at $p < 0.001$;
- h. pt. global comparisons: +2.17 vs. +2.34 vs. +2.82
Evaluation: both ketoprofen dosages superior to placebo at $p < 0.001$;
- i. total score-joint tenderness: -19.7 vs. -15.3 vs. - 9.9
Evaluation: ketoprofen 200 mg/d (but not 300 mg/d) superior to placebo at $p < 0.05$;
- j. total # - joint tenderness: - 9.7 vs. - 9.0 vs. - 6.0
Evaluation: same as in par. i. above;
- k. # mod. & severe - joint tenderness: - 7.0 vs. - 4.7 vs. - 3.5
Evaluation: same as in par. i. and j. above;
- l. total score-joint swelling: -11.0 vs. - 9.0 vs. - 7.1
Evaluation: N.S. intergroup differences;
- m. total # - joint swelling: - 5.8 vs. - 5.0 vs. - 3.9
Evaluation: N.S. intergroup differences;
- n. #mod. & severe - joint swelling: - 4.3 vs. - 2.9 vs. - 2.4
Evaluation: N.S. intergroup differences.

1.1.4.1 Conclusions

- a. In 6/14 variates, both ketoprofen dosages were superior to placebo at $p < 0.001$ (4/6 variates), $p < 0.01$ (1/6 variates), and $p < 0.05$ (1/6 variates).
- b. In 1/14 variates, the 300 mg/d ketoprofen dosage was superior to 200 mg/d and to placebo at $p < 0.05$.
- c. In 3/14 variates, the 200 mg/d (but not the 300 mg/d!) was superior to placebo.
- d. In 4/14 variates, there were no significant intergroup differences; these four variates included measurement of joint swelling (3/4) for which 6-week Rx may have been too short evaluation period, and functional class (1/4) which did not improve significantly in any of these three groups.

1.1.4.2 Summary:

satisfactory improvement was observed in the majority of clinical efficacy variates when ketoprofen was compared to placebo, however, without complete dose proportionality.

1.2. Safety

1.2.1. Number and percentage of ADR

a. less than 250 mg/d ketoprofen

week 1: 15/95 pts. = 15.8%
week 2: 15/93 pts. = 16.1%
week 3: 13/87 pts. = 14.9%
week 4: 8/81 pts. = 9.9%
week 5: 17/75 pts. = 22.7%
week 6: 11/72 pts. = 15.3%.

b. 250 mg/d ketoprofen or more

week 1: 23/86 pts. = 26.7%
week 2: 20/81 pts. = 24.7%
week 3: 19/81 pts. = 23.5%
week 4: 8/74 pts. = 10.8%
week 5: 7/65 pts. = 10.8%
week 6: 6/58 pts. = 10.3%.

1.2.1.1. Conclusions

- a. Clinical ADRs occurred at the arithmetic mean of 15.8% in the less than 250 mg/d ketoprofen group as compared to 17.8% for the more than 250 mg/d ketoprofen group.
- b. While there was significant decrease in the incidence of ADR after the third week in the 250 mg/d, or more of ketoprofen, there was an increase (apparently of borderline significance - L.O.) of the incidence of ADR during the fifth week of the less than 250 mg/d ketoprofen group.

1.2.1.2. Summary

Somewhat more patients reported clinical ADR in the higher dosage ketoprofen group without apparent interdose significance.

1.2.2. Number of patients reporting one or more clinical ADR:

ketoprofen, 200 mg/d vs. ketoprofen, 300 mg/d vs. placebo:
43/97 (= 44.3%) vs. 46/93 (= 49.5%) vs. 39/94 (= 41.5%)

1.2.2.1. Conclusion:

no apparent inter-drug-placebo differences.

1.2.3. Number of dropouts due to clinical ADR

3/97 (= 3.1%) vs. 3/93 (= 3.2%) vs. 3/94 (=3.2%)

Conclusion: obvious non-significance.

1.2.4. Number of patients experiencing specific ADR according to organ systems

	<u>Ketoprofen 200mg/d</u>	<u>Ketoprofen 300mg/d</u>	<u>placebo</u>
neurologic/sensory	13/97(=13.4%)	14/93(15.1%)	13(13.8%)
cardiovascular	0	1 (1.1%)	0
respiratory	1 (1%)	0	0
GI	27 (27.8%)	37(39.8%)	26(27.7%)
GU	2 (2.1%)	1 (1.1%)	1(1.1%)
skin	5 (5.2%)	4 (4.3%)	11(11.7%)
musculoskeletal	0	0	3(3.2%)
general	2 (2.1%)	4 (4.3%)	5(5.3%)

1.2.4.1. Conclusions:

while the percentage of patients affected with GI ADR was slightly higher in the 300 mg/d ketoprofen group, and the skin-related ADR (mostly rash and pruritus) slightly more frequent in the placebo group, none of these differences reached statistical significance.

1.2.4.2. Summary:

I agree with sponsor's conclusions that "At both tested dose levels ketoprofen was therapeutically superior to placebo in the treatment of adult-onset rheumatoid arthritis and displayed a side-effect profile similar to that of placebo."

2. Study MDS-306B: "A Double-Blind Multicenter Comparison of Ketoprofen and Placebo (Administered B.I.D.) In Patients with Rheumatoid Arthritis."

F. X. Burch, M.D., R.M. Fleischmann, M.D., J. W. Griffin, M.D., S.S. Hartman, M.D., B.G., Lanier, M.D., S. Mortensen, M.D., J.S. Spindler, M.D., and P.D. Vreede, M.D.,

administered in a randomized, double-masked and parallel design for 6 weeks at the final dose (i.e., the total duration was 6 weeks in patients who remained at the original dose and 8 or 10 weeks in those whose dosage was increased at week 2 or 4, resp.) either 300 mg/d ketoprofen (50 mg caps., 3 b.i.d.) to 65 patients with adult-onset

R.A. who had been enrolled in other ketoprofen trials (primarily MDS-306A) and had completed at least 6 months of open-label treatment or placebo, to 41 patients. The dosage was to be increased to 400 mg/d ketoprofen (50 mg caps., 4 b.i.d.) or placebo caps. (4 b.i.d.) at visit 2 or 3 (spread 2 weeks apart) if the initial response was judged to be inadequate.

2.1. Demographic data

2.1.1. Ketoprofen: 52F, 13M; age 26-72, mean 50.6; 62 Caucasoid, 2 Negroid, 1 other; mean duration of RA 7.2 y.; stage 1:18, stage 2: 34, stage 3:12, stage 4:1; chrysotherapy: 8.

2.1.2. Placebo: 29F, 12M; age 28-79, mean 56.6 years; 40 Caucasoid, 1 Negroid; mean duration of RA 7.6 years; stage 1:13, stage 2:17, stage 3: 11; chrysotherapy: 7.

2.1.3. Conclusions:

none of these intergroup differences reached statistical significance.

2.2. Summary of maintenance dosage

2.2.1. Ketoprofen

- a. daily dose increased at week 2:
25 (= 38.5%);
- b. daily dose increased at week 4:
6 (= 9.2%);
- c. daily dose unchanged:
 - (1) completed 6 weeks: 27 (= 41.5%);
 - (2) dropped out due to lack of efficacy:
4 (= 6.2%);
 - (3) dropped out due to ADR: 1 (1.5%).
(N.B.: two ketoprofen and one placebo patient had no dosage information).

2.2.2. Placebo

- a. daily dose increased at week 2:
24 (= 58.5%);
- b. daily dose increased at week 4:
5 (= 12.2%);
- c. daily dose unchanged:
 - (1) completed 6 weeks: 9 (= 22.0%);
 - (2) dropped out due to lack of efficacy:
2 (= 4.9%);
 - (3) dropped out due to ADR: 0.

2.3 Summary of significant treatment effects

(ANACOVA, based on main baseline).

- a. 50-foot walking time: $p = 0.018$ in favor of ketoprofen at week 2 of maintenance;
- b. mean grip strength: $p = 0.024$ in favor of ketoprofen at last analyzable visit;
- c. total score of tender joints:
 - (1) week 2: $p = 0.002$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.006$ in favor of ketoprofen;
 - (3) average of all post-baseline visits: $p = 0.015$ in favor of ketoprofen;
- d. # of tender joints; severity (minimal, moderate, severe):
 - (1) week 2: $p = 0.006$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.009$ in favor of ketoprofen;
 - (3) average of all post-baseline visits: $p = 0.017$ in favor of ketoprofen;
- e. # of tender joints severity (moderate, severe):
 - (1) week 2: $p = 0.033$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.026$ in favor of ketoprofen;

- f. total core of swollen joints:
 - (1) week 2: $p = 0.005$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.026$ in favor of ketoprofen.
- g. #of swollen joints severity (moderate, severe):
 - (1) week 2: $p = 0.001$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.009$ in favor of ketoprofen.
 - (3) average of all post-baseline visits: $p = 0.043$ in favor of ketoprofen;
- h. # of swollen joints severity (minimal, moderate, severe) at week 6 of maintenance: $p = 0.026$ in favor of placebo.

2.3.1. Conclusions:

15/16 of the above evaluated variates improved statistically significantly in favor of ketoprofen, while 1/16 improved significantly in favor of placebo.

2.4. Summary of significant treatment effects

(Kruskal-Wallis test, based on main baseline)

- a. mean grip strength
 - (1) week of 6 of maintenance: $p = 0.039$ in favor of ketoprofen.
 - (2) last analyzable : $p = 0.046$ in favor of ketoprofen;
- b. physician's global assessment at week 2: $p = 0.050$ in favor of ketoprofen;
- c. patients global assessment
 - (1) week 2 of maintenance: $p = 0.041$ in favor of ketoprofen;
 - (2) average of all post-baseline visits: $p = 0.026$ in favor of ketoprofen;
- d. Total score of tender joints
 - (1) week 2: $p = 0.017$ in favor of ketoprofen;
 - (2) week 2 of maintenance: $p = 0.033$ in favor of ketoprofen.

e. # of tender joints (minimal, moderate, severe):

(1) week 2: $p = 0.019$ in favor of ketoprofen;

(2) week 2 of maintenance: $p = 0.015$ in favor of ketoprofen;

(3) average of all post-baseline visits: $p = 0.043$ in favor of ketoprofen.

f. Total score of swollen joints (at week 2): $p = 0.036$ in favor of ketoprofen.

2.4.1 Conclusions:

all of the above evaluated variates improved statistically significantly better in favor of ketoprofen.

2.5. Statistically significant determinations from main baseline in the placebo group

<u>Variates</u>	<u>Visit</u>	<u>Mean change from baseline</u>
a. walking time	week 2 of maintenance	1.54 sec up
b. mean grip strength	week 2	20.5 mm Hg dow
	week 2 of maintenance	17.9 mm Hg dow
	week 6 of maintenance	14.8 mm Hg dow
	Average of all p-b visits	16.9 mm Hg ~~dow~~
	last visit	16.9 mm Hg dow
c. morning stiffness	week 2	1.2 h up
	week 2 of maintenance	1.38 h up
	average of all post-baseline visits	1.23 h up
	last visit	1.48 h up
d. functional class	week 6 of maintenance	0.19 down
e. inv. global assessment	week 2	0.44 up
	week 2 of maintenance	0.41 up
	Average of all post-baseline visits	0.36 up
f. pt.'s globas assessment	week 2	0.41 up
	week 2 of maintenance	0.46 up
	week 6 of maintenance	0.41 up
	average of all post-baseline visits	0.48 up
	last visit	0.52 up
g. total score of tender joints	week 2	9.31 up
	week 2 of maintenance	9.65 up
	week 4 of maintenance	6.89 up
	average of all post-baseline visits	10.09 up
	last visit	9.20 up

h. number tender joints (minimal, moderate severe):		
	week 2	3.92 up
	week 2 of maintenance	4.46 up
	week 4 of maintenance	4.25 up
	average of all post-baseline visits	4.73 up
i. number of tender joints (moderate, severe):		
	week 2	3.64 up
	week 2 of maintenance	3.62 up
	week 4 of maintenance	2.64 up
	average of all post-baseline visits	3.82 up
	last visit	3.75 up
j. total score of swollen joints	week 2	3.21 up
k. number of swollen joints severity (minimal, moderate, severe):		
	week 2	1.92 up
	week 2 of maintenance	2.03 up.

2.5.1 Conclusions

all 11/11 clinical efficacy variates deteriorated statistically significantly on placebo at one time or another.

2.6. Summary:

I concur with the sponsor's conclusion that "this study confirms the effectiveness of twice-a-day dosage regimen for ketoprofen (150 or 200 mg b.i.d) in the maintenance therapy" (of R.A. - L.O.).

2.7. Safety

2.7.1 Adverse reactions

The term "Intercurrent Signs and Symptoms" (ISS) has been used in this report since the events recorded by the investigators as ADR also included those which were assessed as "not related" to the test medication.

a. ADR according to organ systems

	ketoprofen (N=65)	placebo (N=41)
neurologic/sensory	7/65 (10.8%)	0
respiratory	1/65 (1.5%)	1/41 (2.4%)
GI	12/65 (18.5%)	4/41 (9.8%)
skin	2/65 (3.1%)	1/41 (2.4%)
general	1/65 (1.5%)	1/41 (2.4%).

Conclusion: after removing the ISS determined to be "unrelated" to the trial drug by the investigators, the association between treatment and the number of patients reporting ISS for each organ system was assessed via Fisher's exact test with no significant intergroup differences observed.

b. Most commonly occurring ADR

- (1) tinnitus: 3/65 pts. (4.6%) 8 times = 3/3% prevalence rate*;
- (2) epigastric pain: 3/65 pts. (4/6%) 7 times - 2.9% prevalence rate;
- (3) dyspepsia: 5/65 pts. (7.7%) 6 times - 2.5% prevalence rate;

*prevalence rate is defined as the # of incidences of a particular type of ISS divided by the total # of patient visits.

Evaluation and conclusion:

when compared with respect to the prevalence of ISS on a patient-to-patient basis (Kruskal-Wallis test), and on inpatient proportions of total visits for which a particular ISS was reported, no statistically significant intergroup differences were observed.

c. Number of patient reporting one or more ISS

22/65 (33.8%) for ketoprofen vs. 7/41 (17.1%) for placebo:
 $p = 0.07$.

Evaluation: more patients reported one or more ISS at borderline significance on ketoprofen than on placebo.

d. Number of dropouts due to ISS:

3/65 (4/9%) for ketoprofen vs. 0 for placebo: $p = 0.28$.

Evaluation: no statistically significant intergroup difference in incidence of dropouts due to ISS (ADR).

e. Vital signs and body weight

except for minor, clinically insignificant body weight changes, there were no statistically significant intergroup differences in pulse, systolic and diastolic BP at any of the evaluation points.

f. laboratory variates

Introductory remark: since the statistical inference about laboratory tests by the ANACOVA (analysis of covariance) was almost identical to that of the Kruskal-Wallis test, only the results of ANACOVA, reflecting the mean change from baseline at the average of all post-baseline visits, are discussed in the following.

(1) Hemoglobin (g%)

-0.22 for ketoprofen vs. 0.30 for placebo: $p < 0.001$.

Conclusion: statistical but no clinical inter-group difference.

(2) Hematocrit (%)

-0.49 for ketoprofen vs. 0.69 for placebo: $p < 0.01$.

Conclusion: same as in par. (1) above.

(3) SUA: (mg%)

-0.28 for ketoprofen vs. 0.23 for placebo: $p < 0.001$.

Conclusion: same as in par. (1) and (2) above.

(4) BUN (mg%)

-0.13 for ketoprofen vs. -2.74 for placebo: $p < 0.01$.

Conclusion: same as in par. (1) through (3) above but why should mean BUN fall by 2.74 mg % in the placebo group?!

(5) Total serum protein (Gm%)

-0.12 for ketoprofen vs. 0.10 for placebo: $p < 0.001$.

Conclusion: same as in par. (1) through (3) above.

(6) WBC, lymphocytes, neutrophils, serum creatinine and serum total bilirubin (all by Kruskal-Wallis test): no statistically significant intergroup differences at average of all post-baseline visits.

ff. Evaluation of laboratory variates

some statistically - but not clinically - significant intergroup differences were found in Hb, Hct, SUA, BUN, and total serum protein in favor of placebo.

3. Study MSD - 226: "A Double-Blind Multicenter Study of Compare the Efficacy and Safety of Ketoprofen with Placebo, When Administered Concomitantly with Steroids, in Rheumatoid Arthritis."

P.A. April, M.D., M. L. Brandon, M.D., B. K. Guerin, M.D., E. H. Krick, M.D., J. L. McMillen, M.D., J. E. Peckley, M.D., L. M. Seebach, M.D., and C. Seward, M.D. administered in a randomized, double-masked and parallel design for 24 weeks either ketoprofen, initially 50 mg t.i.d. - which could be adjusted to an upper limit of 300 mg/d or to a lower limit of 100 mg/d (71 pts.) or placebo (74 pts.) to 145 patients with active, definite or classical R.A. who were maintained on corticosteroid therapy, not exceeding the equivalent of 15 mg of prednisone per day. 92/145 pts. completed satisfactorily the 24-week drug administration 43/92 in the ketoprofen group (28F, 15M), age 29-82, mean 56.2 years, mean duration of R.A. 12.8 years, 14/43 on concomitant chrysotherapy) as compared to 49/92 in the placebo groups (39F, 10M, age 28-85, mean 56.4 years, mean duration of R.A. 13.1 years, 14/49 on concomitant chrysotherapy).

3.1. Premature termination

a. Lack of efficacy

26/71 (36.6%) ketoprofen vs. 35/74 (47.3%) placebo;

b. ADR:

2/71 (2.8%) ketoprofen vs. 3/74 (4.1%) placebo;

c. other reasons:

5/71 (7.0%) ketoprofen vs. 5/74 (6.8%) placebo;

d. total dropouts:

33/71 (46.5%) ketoprofen vs. 43/74 (58.1%) placebo.

ad b/The dropouts in the ketoprofen group were due to urticaria, and abdominal pain with headache;
the dropouts in the placebo group were due to peptic ulcer, epigastric pain with dyspepsia, and dyspepsia.

- e. Of the 92 patients who were not completely excluded from efficacy analysis, only 70 were efficacy-analyzable at their last actual visits; the dropouts of this subset were:

(1) due to lack of efficacy:

8/32 (=25.0%) ketoprofen vs. 24/38 (=63.2%) placebo
($p < 0.004$);

(2) due to ADR:

0/32 ketoprofen vs. 1/38 placebo.

ad e/ most of these dropouts were due to acute illnesses unrelated to the drug (or placebo).

3.2. Medication consumption and compliance

The drug consumption was determined by capsule count at each visit. Ketoprofen patients took an average of 216.2 mg (4.3 capsules) per day and placebo patients 4.6 capsules per day (whole population).

3.3. Efficacy assessment

A total of 145 patients entered the trial. One investigator (Bernard K. Querin, M.D.), apparently misunderstood the protocol to be a "steroid - sparing" trial; due to numerous violations of the requirement of a stable background medication, his entire group (21 pts.) was excluded from efficacy analysis. In addition, 27 patients were excluded for the following reasons:

7/27 for insufficient consumption of the trial drug;

12/27 for insufficient washout period (positive FeCl_3 test);

3/27 prednisone or chrysotherapy-related protocol violations;

2/27 no follow-up;

2/27 continued use of analgesics throughout the study;

1/27 misdiagnosis.

Thus, only 97 of the 145 total patients entered into the trial were efficacy-analyzable; however, there were only 5 patients in Dr. McMillen's sample and one of these was excluded from analysis for protocol violation; it was believed that what remained of his sample (4 pts.) would cause undue statistical significance, i.e., the statistical analyses to be performed were not weighted against sample size. Therefore, there were only 92 efficacy-analyzable patients:

43 for ketoprofen, 49 for placebo.

The population was divided at baseline by Functional Class into either Stratum A (Class 1 or 2) or, Stratum B (Class 3 or 4); only one significant difference ($p < 0.01$) between the treatment groups was found at baseline in Stratum A for the number of moderately or severely tender joints.

3.3.1. Functional Class 1 or 2 (Stratum A) (58 analyzable pts., 27/58 for ketoprofen):

a. average visit

5/11 variates improved significantly from baseline in the ketoprofen group compared to 4/11 variates in the placebo group;

b. last visit

3/11 variates in the ketoprofen vs. 2/11 in the placebo group (in addition, walking time, not improved significantly in the ketoprofen group, deteriorated in the placebo-treated patients).

3.3.2. Functional Class 3 or 4 (more severely ill pts) (34 analyzable pts; 16/34 for ketoprofen):

a. average visit

7/11 variates improved significantly from baseline in the ketoprofen group compared to 0/11 in the placebo group; in 6/7 variates, there was statistically significant intergroup difference in favor of ketoprofen;

b. last visit

6/11 variates in the ketoprofen vs. 0/11 in the placebo group; in all 6/6 variates, there was also a statistically significant intergroup difference in favor of ketoprofen; in addition, the moderately and severely tender joints, which improved in the ketoprofen group at $p < 0.05$ from baseline, deteriorated in the placebo group, thus favoring ketoprofen at $p < 0.001$.

3.3.3. Summary of clinical improvement

The more severely ill patients (Stratum B) improved statistically significantly more in the ketoprofen-treated group as compared to placebo-treated patients, both at the average and at the last visit (24-week).

There were no statistically significant intergroup differences in any variate at week 4.

3.4. Safety assessment

3.4.1. Vital signs and body weight: mean values ketoprofen vs. placebo:

- a. weight: baseline vs. week 24 ketoprofen = 147.9 vs. 152.8 compared to baseline vs. week 24 placebo = 143.0 vs. 146.0;
- b. pulse: 77.1 vs. 79.5 ketoprofen compared to 80.9 vs. 78.0 placebo;
- c. syst. BP: 131.3 vs. 132.0 ketoprofen compared to 128.4 vs 125 placebo;
- d. diast. BP 78.7 vs. 79.2 ketoprofen compared to 78.4 vs. 75.8 placebo.

3.4.1.1. Conclusion: there were no statistically or clinically significant inter- and intragroup differences in regard to vital signs and body weight.

3.4.2. Laboratory variates

a. Hemoglobin

clinically significant, i.e., defined as drop of 2g% (or more), drops of hemoglobin means occurred in the ketoprofen group with statistical significance of $p = 0.044$ at week 12, $p = 0.043$ at week 16, $p = 0.012$ at week 20, but were statistically significant at weeks 2, 4, 8, and 24 (last).

a.(1). Conclusion:

unexplained drop of hemoglobin values at weeks 12, 16, and 20, but not at weeks 2, 4, 8, and 24 (last).

b. Hematocrit

a clinically possibly significant, i.e., 5-10% reduction, of hematocrit means occurred at $p = 0.028$ at week 16, but not at any other weeks (2, 4, 8, 12, 20, and 24).

b.(1) Conclusion

unexperienced drop of mean hematocrit value at week 16.

c. Biochemical variates

There 12 other changes - all inconsistent in the ketoprofen - treated group compared to 14 other (inconsistent, too) changes in the placebo-treated group.

d. ADR, clinical prevalence rate of ketoprofen vs. placebo:

(1) neurologic - sensory

nervousness:	0.27 vs. 0.62 (placebo)
dizziness:	0.55 vs. 0
insomnia:	0.27 vs. 0.31
headache:	0.82 vs. 0.82
deafness, transitory, partial:	0.27 vs. 0
vertigo:	0.27 vs. 0
tinnitus:	0 vs. 2.46
keratoconjunctivitis:	0.27 vs. 0.31
taste perversion:	0.27 ketopr. vs. 0 placebo;

(2) cardiovascular

palpitation:	0.82 vs. 0
vasodilation:	0.55 vs. 0

(3) respiratory

sinusitis:	0.55 vs. 0
pharyngitis:	0.55 vs. 0

(4) GI

nausea and vomiting:	1.09 vs. 0.82
flatulence:	0.82 vs. 0.82
epigastric pain:	0.82 vs. 0.31
dyspepsia:	3.56 vs. 1.23
nausea:	1.09 vs. 1.23
abdominal pain:	0.55 vs. 0
diarrhea:	0.27 vs. 5.23(!)
constipation:	1.64 vs. 0.62
peptic ulcer:	0.55 vs. 0.31
rectal pain:	0.27 vs. 0
increased appetite:	0 vs. 0.31
anorexia:	0 vs. 0.82
vomiting:	0 vs. 0.31

(5) GU

dysuria:	0.27 vs. 0.31
pollakisuria:	0.27 vs. 0.62

(6) Skin

urticaria:	0.27 vs. 0
"other"	0.27 vs. 0
pruritus	0 vs. 0.31
eczema:	0 vs. 0.62
vesico-bullous rash:	0 vs. 0.31
alopecia:	0 (ketoprofen) vs. 0.31 (placebo)
nonspecified rash:	0 vs. 0.82
erythematous rash:	0 vs. 0.31

(7) General ADR

sweating:	0.55 vs. 0
weight increases:	0.27 vs. 0
peripheral edema:	1.37 vs. 0
infection:	0.55 vs. 0.62
weight decrease:	0 vs. 0.82
malaise:	0 vs. 0.31

d(1) Conclusion

dyspepsia was seen significantly more frequently ($p=0.02$) in the ketoprofen group, while diarrhea was reported significantly more frequently ($p=0.01$) in the placebo group.

e. Total # of patients reporting one or more ADR:

34/71 (47.9%) in the ketoprofen group vs. 33/74 (44.6%) in the placebo-treated group.

e(1) Conclusion

obviously no significant intergroup differences.

f. Number of dropouts due to ADR:

2/71 (2.8%) ketoprofen vs. 3/74 (4.1%) placebo (N.S.).

Remarks: the dropouts in the ketoprofen group were due to urticaria and abdominal pain, resp., and in the placebo group to dyspepsia (2 pts.) and peptic ulcer, resp.; the latter ADR was probably due to the concomitant corticosteroid therapy or to the intake of other NSAID in violation of the protocol.

3.4.3. Summary of safety assessment

- a. No statistically or clinically significant intergroup differences were found in regard to vital signs, body weight and laboratory variates.
- b. With the exception of statistically significantly higher incidence of dyspepsia in the ketoprofen group and diarrhea in the placebo group, there were no significant intergroup differences in regard to the incidence of clinical ADR.

4. Study MDS-201: "A Double-Blind Multi-center Study to Compare the Efficacy and Safety of Ketoprofen with ASA in Rheumatoid Arthritis."

S. J. Alexander, M.D., P. J. Bilka, M.D., A. Calin, M.D., G. E. Ehrlich, M.D., A. L. Goldman, M.D., E. H. Krick, M.D., H. E. Montoya, M.D., J. L. Parsons, M.D., and F. R. Schmid, M.D. administered in a randomized, double - masked and parallel design for 54 weeks either ketoprofen, initially 50 mg q.i.d. which could be adjusted to 75 mg q.i.d. or 25 mg q.i.d. (115 patients), or aspirin, initially 900 mg q.i.d. which could be adjusted to 1350 mg q.i.d. or 450 mg q.i.d. (114 patients) to a total of 229 patients with active, definite or classical R.A., 160F, 69M, age 25-81, mean 53.1 years, with the duration of the disease from 1 to 57, mean 10.5 years, stage 1 36/229, stage 2 108/229, stage 3 65/229, stage 4 12/229. While there were no statistically significant intergroup differences in regard to age, sex, or duration of R.A., there was more advanced disease at baseline in the ketoprofen group (stages 3 and 4: 46 ketoprofen vs. 31 aspirin, $p < 0.05$).

4.1. Concomitant medication

The ketoprofen - treated patients received significantly ($p = 0.018$) more concomitant medication than the aspirin treated group: chrysotherapy: 45 vs. 30; antimalarials: 5:1; none: 65 vs. 81.

Two steroid-treated patients (both in the aspirin group) were excluded from efficacy analysis.

The more prevalent use of longacting antirheumatic agents in the ketoprofen group is in accordance with more advanced disease by anatomic criteria (v. supra.).

4.2. Dropouts

71/115 (61.7%) patients in the ketoprofen and 69/114 (60.5%) patients in the aspirin group did not complete the study.

a. Lack of efficacy

37/115 (32.2%) ketoprofen vs. 19/114 (16.7%) aspirin.

b. ADR

11/115 (9.6%) ketoprofen vs. 20/114 (17.5%) aspirin.

c. Lack of efficacy and ADR

3/115 (2.6%) ketoprofen vs. 12/114 (10.5%) aspirin.

N.B.: a. thru c. totals to: 51/115 (44.3%) ketoprofen vs. 51/114 (44.7%) aspirin.

4.2.1. Conclusion

There were no statistically significant interdrug differences in regard to the total incidence of dropouts due to lack of efficacy (40/115 ketoprofen vs. 31/114 aspirin, $p > 0.05$), while there were statistically significantly more dropouts due to ADR in the aspirin - treated patients [32/114 (28.1%) aspirin vs. 14/115 (12.29%) ketoprofen, $p < 0.01$].

4.3. Drug consumption and compliance

In the whole study population, patients took an average of 246.4 mg/d of ketoprofen or 4.03 g/d of aspirin, i.e., in general, the patients complied with the trial medication as prescribed.

4.4. Efficacy assessment

4.4.1. Exclusions from efficacy evaluation

51/229 patients were excluded (22/115 ketoprofen, 29/114 aspirin) for the following reasons (in decreasing order of frequency):

noncompliance with a sufficient dose of trial medication;

change in the regimen of disease-modifying antirheumatic drugs;

ingestion of medications prohibited by the protocol;

failure to meet the entry criteria or diagnostic error; and

no follow-up visits within an acceptable time since taking the study medication.

The number of patients therefore evaluated for efficacy was 178, 93/178 for ketoprofen, 85/178 for aspirin.

In addition, in 85/178 analyzable patients (42/85 ketoprofen, 43/85 aspirin), certain visits were excluded from efficacy analysis, mostly for noncompliance, protocol violations or multiple visits within a time interval.

4.4.2. Efficacy variates

All of the following 12 efficacy variates, namely, 50-foot walking time; functional class; mean grip strength; morning stiffness duration; global assessment by the patient; total score of all tender joints; number of minimally, moderately and severely tender joints; number of moderately and severely swollen joints; and number of moderately and severely swollen joints, improved statistically significantly from baseline at all evaluation periods (weeks 2, 4, 12, 24, 54, average, last visit) for both drugs with the exception of functional class at weeks 54 and/or last visit for the ketoprofen - treated patients. The preponderant significance of these improvements was $p < 0.001$ for both drugs.

With the exception of the assessment by the patients at weeks 4 and the last visits (in favor of aspirin), there were no significant interdrug differences in the remaining 166/168 variates x evaluation periods.

4.5. Safety assessment

the following are the mean values, baseline - week 54, ketoprofen vs. aspirin:

4.5.1. Body weight

149.33 - 155.97 vs. 151.77 - 152.21 (N.S.).

4.5.2. Pulse rate

82.15 - 83.35 vs. 80.08 - 76.88 (N.S.).

4.5.3. Systolic BP

125.84 - 122.44 vs. 128.21 - 125.31 (N.S.).

4.5.4. Diastolic BP

78.27 - 80.21 vs. 77.92 - 76.02 (N.S.).

Conclusion

there were neither intra - nor inter-group statistically significant differences in regard to vital signs, when baseline means were compared to 54-week means.

4.5.5. Laboratory variates

a. Neutrophils

for ketoprofen, there were 2 increases vs. 12 decreases at week 12 at $p=0.007$ (no significant changes in the aspirin treated group).

b. Lymphocytes

for ketoprofen, there were 14 increases and 6 decreases at week 12 at $p=0.058$, and 4 increases and 11 decreases at week 24 at $p=0.059$ (no significant changes in the aspirin group).

c. Eosinophils

for ketoprofen, there were 17 increases and 6 decreases at week 6 at $p=0.017$, and for aspirin, 21 increases and 11 increases at week 12 at $p=0.055$.

d. Basophils

for ketoprofen, there were 4 increases at week 24 at $p=0.063$ and 5 increases at week 36 at $p=0.031$ (no significant changes in the aspirin-treated group).

e. Hemoglobin

for ketoprofen, there were 6 elevations and 16 decreases at week 2 at $p=0.026$, 3 elevations and 21 decreases at week 4 at $p=0.001$, 5 elevations and 14 decreases at week 8 at $p=0.032$, 7 elevations and 15 decreases at week 12 at $p=0.067$;

for aspirin, there were 5 elevations and 18 decreases at week 2 at $p=0.005$, 5 elevations and 13 decreases at week 4 at $p=0.048$, one elevation and 8 decreases at week 12 at $p=0.02$.

f. Hematocrit

for ketoprofen, there were 5 increases and 18 decreases at week 4 at $p=0.005$;

for aspirin, there were 6 increases and 18 decreases at week 2 at $p=0.011$, 7 increases and 16 decreases at week 4 at $p=0.047$, 2 increases and 8 decreases at week 54 at $p=0.055$.

g. ESR

for ketoprofen, there were 3 elevations and 10 decreases at week 12 at $p=0.046$;

for aspirin, there were significant in- and decreases at weeks 2, 4, 6, 12, 24, 36, and 54 at p ranging from 0.046 to $p=0.001$.

h. Urinary WBC

for ketoprofen, there were 3 increases and 11 decreases (from N to L, H to N, or H to L) at week 6 at $p=0.029$;

for aspirin, there were 5 increases and 16 decreases at week 4 at $p=0.013$, 4 increases and 15 decreases at week 6 at $p=0.01$.

i. Urinary albumin

for ketoprofen, there were 5 decreases at week 6 at $p=0.031$;

for aspirin, there were 4 decreases at week 24 at $p=0.063$.

j. SUA

for ketoprofen, there were 3 elevations and 14 decreases at week 2 at $p=0.006$, one elevation and 9 decreases at week 54 at $p=0.011$;

for aspirin, there were significant in- and decreases at all elevation periods at p ranging from 0.002 to 0.001.

k. Total serum protein

for ketoprofen, there were 4 decreases at week 12 at $p=0.063$, one increase and 6 decreases at week 24 at $p=0.063$, too. (no significant changes in the aspirin group).

l. SAP

in the ketoprofen group, there was one elevation and 5 decreases at week 2 at $p=0.063$;

for aspirin, there were 3 increases and 9 decreases at week 2 at $p=0.073$, 8 decreases at week 4 at $p=0.004$, one increase and 8 decreases at week 6 at $p=0.02$, 3 increases and 9 decreases at 8 and 12, both at $p=0.073$.

m. In addition, there were following changes in the aspirin-treated group only:

- (1) significant increase of specific urinary gravity at weeks 6, 8, and 12;
- (2) significant elevations of BUN at weeks 2, 4, 6, 8, and 12;
- (3) significant elevations of LDH at week 2, 4, 8, and 54.
- (4) significant elevation of SGOT at week 4.

4.5.6. Clinical ADR (total)

prevalence rate in % - ketoprofen vs. aspirin, and significance:

a. Neurologic/sensory

depression:	0.11 vs. 0.63 at $p=0.18$
nervousness:	0.22 vs. 0.52 at $p=0.322$
dizziness:	0.44 vs. 1.15 at $p=0.244$
semnolence:	0.55 vs. 0.84 at $p=0.484$
headache:	0.33 vs. 1.57 at $p=0.131$
deafness, v. s., partial:	0.11 vs. 3.67 at $p < 0.001$
tinnitus:	2.22 vs. 8.60 at $p < 0.001$
vision abnormality:	0.44 vs. 0.52 at $p=0.654$.

b. GI

anorexia:	0.22 vs. 0.52 at $p=1.0 (!)$
dry mouth:	-- vs. 1.05 at $p=0.025$
stomatitis:	0.33 vs. 0.52 at $p=0.66$
eructation:	1.55 vs. 1.05 at $p=0.134$
flatulence:	1.11 vs. 1.05 at $p=0.523$
dyspepsia:	2.77 vs. 8.28 at $p = 0.001$
epig. pain:	0.33 vs. 2.52 at $p=0.002$
nausea:	2.33 vs. 3.25 at $p=0.4$
abd. pain:	1.11 vs. 1.05 at $p=1.0$
diarrhea:	0.44 vs. 0.63 at $p=0.726$
constipation:	0.89 vs. 2.94 at $p < 0.05$ (L.O.)
gastritis:	0.11 vs. 0.52 at $p=0.31$.

c. Skin

pruritus: 0.11 vs. 1.36 at $p=0.06$
mousspec. rash: 0.11 vs. 0.84 at $p=0.054$

d. General

weight increase: -- vs. 0.94 at $p=0.026$
asthenia: 1.11 vs. 0.94 at $p=0.31$
periph. edema: 1.11 vs. 0.10 at $p=0.181$
gen. edema: 0.55 vs. --- at $p=0.084$.

Conclusion

7/26 ADR occurred statistically significantly more in the aspirin treated group: transient and partial deafness, tinnitus, dry mouth, dyspepsia, epigastric pain, constipation, and weight increase.

There were no statistically significant intergroup differences in the prevalence of the remaining 19/26 ADR.

4.5.7 Clinical ADR (moderate or severe)

a. Neurologic/sensory

- (1) 16 pts. for ketoprofen vs. 37 pts. for aspirin at $p=0.002$;
- (2) Average proportion of moderate or severe ADR to total number of patient visits was 0.07 for ketoprofen vs. 0.12 for aspirin at $p < 0.001$.

b. GI

- (1) 13 pts. for ketoprofen vs. 33 pts. for aspirin at $p=0.024$;
- (2) Average proportion of moderate or severe ADR to total number of patient visits was 0.09 for ketoprofen vs. 0.17 for aspirin at $p=0.012$.

Conclusion:

in 2/3 organ systems, more patients reported more ADR in the aspirin-treated group than in the ketoprofen-treated group in statistically significant difference (neurologic/sensory and gastrointestinal ADR).

There were no statistically significant intergroup differences in the remaining 7/9 organ systems ADR.

5. Study MSD - 270: "A Double-Blind Multicenter Study to Compare the Efficacy and Safety of Ketoprofen with ASA in Rheumatoid Arthritis."

M. Gamarra, M.D., A.L. Goldman, M.D., M. O'Hanlan, M.D., C. W. Seward, M.D., and H. C. Tretbar, M.D. administered in a randomized, double-masked and parallel design for 24 weeks either ketoprofen initially 50 mg q.i.d. which could be adjusted to 75 mg q.i.d. or 25 mg q.i.d. (41 patients), or aspirin, initially 900 mg q.i.d. which could be adjusted to 1350 mg q.i.d. or 450 mg q.i.d. (40 patients) to a total of 81 patients with active, definite or classical R.A., 59F, 22M, age 25-75, mean 54.5 years, with mean R.A. duration of 9.1 years. There were 32/41 F in the ketoprofen group and 27/40 in the aspirin group.

5.1. Concomitant antirheumatic therapy ketoprofen vs. aspirin

- a. chrysotherapy: 9 vs. 9
- b. antimalarials: 2 vs. 3
- c. corticosteroids: 10 vs. 8
- d. chrysotherapy and steroids: 3 vs. 3
- e. antimalarials and steroids: 4 vs. 3
- f. chrysotherapy and antimalarials + steroids: 2 vs. 1.

Conclusion: no statistically significant interdrug differences in regard to concomitant antirheumatic therapy.

5.2. Premature termination

a. Lack of efficacy

5/41 (12.2%) ketoprofen vs. 4/40 (10.0%) aspirin.

b. ADR:

3/41 (7.3%) ketoprofen vs. 8/40 (20.0%) aspirin (p 0.05 in favor of ketoprofen).

c. Other reasons: 3/41 (7.3%) ketoprofen vs. 6/40 (15.0%) aspirin.

ad b: the dropouts in the ketoprofen group were due to dyspepsia, petechial rash, and pruritus with petechial rash;

the dropouts in the aspirin group were due to epigastric pain (2/8), headache, peptic ulcer, dyspepsia, vomiting (2/8), and occult blood in stool.

Conclusion

statistically significantly more patients dropped out prematurely due to clinical ADR in the aspirin-treated group than in the ketoprofen-treated group.

5.3. Medication consumption and compliance

The drug consumption was determined by capsule count at each visit.

Ketoprofen patients took a mean daily dose of 247.3 mg compared to 3.805 g of the aspirin patients.

5.4. Efficacy assessment

10/81 patients (3/10 ketoprofen, 7/10 aspirin) were excluded from efficacy analysis for noncompliance with the protocol requirements. In addition, in 21/71 efficacy-analyzable patients (5/21 ketoprofen, 16/21 aspirin), certain visits were excluded from efficacy evaluation, mostly for noncompliance.

5.4.1. Functional class - improvement from baseline at (last) week 24

$p < 0.001$ for ketoprofen vs. $p < 0.05$ for aspirin.

5.4.2. 50-feet walking time (baseline - week 24)

same as in par. 5.4.1.

5.4.3. Mean grip strength (impr. from baseline to week 24)

same as in par. 5.4.1. and 5.4.2.

5.4.4. Morning stiffness duration (baseline to week 24)

$p < 0.001$ for ketoprofen vs. $p < 0.01$ for aspirin.

5.4.5. Investigator's global assessment (baseline to wk. 24).

$p < 0.001$ for both drugs.

5.4.6. Patient's global assessment (baseline at week 24)

$p < 0.001$ for ketoprofen vs. $p < 0.01$ for aspirin.

5.4.7. Number of moderately and severely tender joints (6. - wk 24)

same as in par. 5.4.6.

5.4.8. Total score of moderately and severely tender joints:

same as in par. 5.4.6. and 5.4.7.

5.4.9. Number of moderately and severely swollen joints:

same as in par. 5.4.6/7/8 above.

5.4.10. Total score of moderately and severely swollen joints
(baseline to week 24)

p 0.001 for both drugs.

Conclusion:

all 10/10 efficacy variates improved statistically significantly from baseline at (last) week 24 for both drugs without significant interdrug differences.

(N.B.: There was only one significant interdrug difference - in favor of ketoprofen - in number of moderately and severely tender joints at week 16).

5.4.11. Improvement of four predefined variates - mean grip strength, morning stiffness duration, investigator's global assessment, patient's global assessment - from baseline to last visit:

percentage of improved pts. - ketoprofen N=38, aspirin N=33 (figures in parentheses indicate percentages of patients showing moderate or marked improvement):

a. Investigator's global assessment

71.0% (13.1%) ketoprofen vs. 78.7% (6.0%) aspirin.

b. Patient's global assessment

71.0% (23.6%) ketoprofen vs. 60.6% (12.1%) aspirin.

c. Grip strength

57.8% ketoprofen vs. 72.7% aspirin.

d. Morning stiffness duration

78.9% ketoprofen vs. 72.7% aspirin.

Conclusion

significant improvements from baseline to last visits in all four efficacy variates without statistically significant intergroup differences.

N.B. Global assessments of disease by investigator and by patient are the most powerful measurement of rheumatoid disease activity (ref. on request - L.O.).

5.5. Safety assessment

5.5.1. Vital signs:

a. Systolic BP

the following are the mean changes for ketoprofen treated patients:

week 12: -6.4 mm Hg at $p=0.016$
week 16: -5.6 mm Hg at $p=0.042$
week 24: -6.9 mm Hg at $p=0.038$.

b. Diastolic BP

(1) the following are the mean changes for the ketoprofen group:

week 8: -3.5 mm Hg at $p=0.007$
week 12: -4.0 mm Hg at $p=0.018$
week 16: -5.6 mm Hg at $p=0.003$
week 20: -4.7 mm Hg at $p=0.021$
week 24: -5.1 mm Hg at $p=0.012$

(2) The following is the mean change for the aspirin group:

-4.3 at $p=0.013$ at week 12 (only).

Conclusion:

the BP changes were statistically but not clinically significant.

c. Weight and pulse:

No statistically significant interdrug differences found.

5.5.2. Laboratory variates

a. Hemoglobin

statistically - not clinically - significant decreases occurred in the ketoprofen patients at weeks 8 ($p < 0.008$), 12 ($p < 0.006$), 16 ($p < 0.002$), and 20 ($p < 0.031$) but not in the aspirin treated group; these differences were statistically significant in favor of aspirin at weeks 8 ($p < 0.029$) and 16 ($p < 0.002$).

- a. (1) Conclusion: no clinically significant interdrug differences in regard to hemoglobin values.

b. Hematocrit

statistically - not clinically - significant decreases occurred in the ketoprofen patients at weeks 12, 16, and 24 ($p: < 0.001, < 0.004, < 0.031$, resp.) but not in the aspirin patients; these interdrug differences were statistically significant in favor of aspirin at weeks 12 ($p < 0.005$), 16 ($p < 0.005$), and 24 ($p < 0.029$).

- b. (2) Conclusion: no clinically significant interdrug differences in regard to Hct values.

c. Eosinophils

at week 4, the eosinophils decreased statistically significantly more in the ketoprofen - than in the aspirin - treated group. This decrease had no clinical significance.

d. Biochemical variates

the fluctuations in the biochemical variates had some minimal statistical, but no clinical significance, whatsoever.

5.5.3. Clinical ADR

prevalence rate of ketoprofen vs. aspirin:

a. Neurologic/sensory

nervousness:	0.24 vs. 0
anxiety:	0.24 vs. 0
dizziness:	0.24 vs. 0.81
insomnia:	0.24 vs. 0
headache:	1.22 vs. 2.43
somnolence:	0 vs. 0.54
ear pain:	0 vs. 0.27
trans., portal deafness:	0 vs. 1.62
tinnitus:	0 vs. 9.19
taste perversion:	0 vs. 0.54.

b. Cardio-vascular

tachycardia: 0.24 vs. 0
vasodilation: 1.22 vs. 0
right heart failure: 0 vs. 0.54

c. GI

anorexia: 0.24 vs. 0.27
gingivitis: 0.24 vs. 0
flatulence: 2.20 vs. 3.24
epig. pain: 0.73 vs. 3.51
dyspepsia: 5.13 vs. 10.54
nausea: 0.49 vs. 2.43
vomiting: 1.22 vs. 1.62
abd. pain: 1.47 vs. 1.89
diarrhea: 0.73 vs. 0.54
constipation: 0.49 vs. 1.89
gastritis: 0.24 vs. 0
rect. hemorrhage: 0.24 vs. 0
peptic ulcer: 0 vs. 0.27
occult blood stool: 0 vs. 0.54.

d. Geritourinary

U.T.I.: 0.24 vs. 0
"other": 0 vs. 1.08.

e. Skin

pruritus: 1.22 vs. 0.54
petechial rash: 0.49 vs. 0
purpuric rash: 0.24 vs. 0
erythematous rash: 0.49 vs. 0.54
eczema: 0 vs. 0.27
alopecia: 0 vs. 0.27.

f. General (ADR)

sweating: 1.22 vs. 0
chills: 0.24 vs. 0
peripheral edema: 1.47 vs. 0.27
infection: 0 vs. 1.08.

Conclusion

Except for the significantly higher incidence of tinnitus - and possibly of dyspepsia - in the aspirin-treated group, there were no statistically significant interdrug differences in regard to clinical adverse reactions.

5.5.3.1. Comparison of moderate or severe ADR

Only in 1/9 organ systems was there any significant interdrug difference: moderate to severe GI ADR occurred in 8 ketoprofen vs. 21 aspirin patients ($p=0.003$); the average proportion of moderate or severe ADR to total number of patient visits was: 0.09 ketoprofen vs. 0.16 aspirin ($p=0.019$).

No statistically significant interdrug differences were observed for these variates in the remaining 8/9 organ systems.

N.B.: when the sponsor analyzed specifically "moderate or severe drug-related intercurrent signs and symptoms" statistically significantly more neurologic/sensory ADR occurred in the aspirin-treated patients (1 vs. 7, $p=0.03$), in addition to (the already mentioned above) GI organ system.

5.5.4. Summary of safety assessment

- a. Some statistically - but not clinically - significant drops of systolic and diastolic blood pressure occurred in the ketoprofen - but not in the aspirin - treated patients.
- b. Some statistically - but not clinically - significant drops of hemoglobin and hematocrit occurred in the ketoprofen and the aspirin treated patients; there were no clinically significant interdrug differences in regard to both of these variates.
- c. With the exception of the significantly higher incidence of tinnitus (and possibly dyspepsia) in the aspirin - treated patients, there were no statistically significant interdrug differences in regard to clinical adverse reactions.

6. Study MDS-210: "A Double-Blind Parallel Comparative Evaluation of the Efficacy and Safety of Ketoprofen versus Indomethacin in the Treatment of Rheumatoid Arthritis." J. R. Caldwell, M.D., B. F. Germain, M.D., S. H. Laurie, M.D., G. E. McLaughlin, M.D., J. E. Pooley, M.D., P. D. Vreede, M.D., and C. H. Wilson, M.D. administered in a randomized, double-masked and parallel design for 12 weeks either ketoprofen, initially 50 mg q.i.d. which could be adjusted to 300 mg/d or 150 mg/d (70 patients), or indomethacin, initially 25 mg q.i.d. which could be adjusted to 150 mg/d or 75 mg/d (70 pts.) to a total of 140 patients with active, definite or classical R.A., 99F, 41M, age 23-82, mean 51.6 years with the mean duration of RA of 8.3 years. There were 53/70F in the ketoprofen, and 46/70F in the indomethacin group. More than 50% of these patients have been previously treated with aspirin, and/or ibuprofen, indomethacin, or naproxen.

40/140 were on concomitant chrysotherapy: 22/40 ketoprofen, 18/40 indomethacin pts; 0/70 ketoprofen and 3/70 indomethacin-treated patients were taking concurrently antimalarials.

6.1. Premature termination

a. Lack of efficacy

8/70 (11.4%) ketoprofen vs. 4/70 (5.7%) indomethacin.

b. ADR

The dropouts in the ketoprofen group were due to vomiting (2/8), headache (2/8), dyspepsia (2/8), cataract and confusion (1/8), and urticaria (1/8).

The dropouts in the indomethacin group were due to headache (2/4), dyspepsia, and diarrhea.

c. Other reasons: 0 ketoprofen vs. 1/70 indomethacin.

6.2 Medication consumption and compliance

Actual drug consumption was determined by capsule count at each visit. Ketoprofen patients took a mean daily dose of 223 mg compared to 113 mg of the indomethacin patients.

6.3. Efficacy assessment

7/140 patients (4/7 ketoprofen, 3/7 indomethacin pts.) were excluded from the efficacy analysis for either not meeting the protocol requirements (5/7) or not complying with the minimum dose throughout the trial.

In addition, in 29/133 analyzable patients (12/29 ketoprofen), 17/29 indomethacin), certain visits were excluded from efficacy analysis most for noncompliance or excessive visits within a time interval, which usually resulted from missing a visit in another time interval.

6.3.1 Functional class

while both drug groups were statistically significantly improved from baseline at the last (12) week, there was statistically significant improvement of the functional class in favor of ketoprofen at $p < 0.05$ at weeks 1 and 12.

6.3.2. Total score of swollen joints

with the exception of week 1 (in favor of ketoprofen at $p = 0.05$), there were no statistically significant interdrug differences at any of the visits (i.e., 2, 4, 8, and 12 weeks).

6.3.3. Global assessment by the investigators

54 improved vs. 12 not improved for ketoprofen compared to 44 improved vs. 23 not improved for indomethacin: $p = 0.048$ in favor of ketoprofen.

6.3.4. Global assessment by the patients

45 improved vs. 21 not improved for ketoprofen compared to 35 improved vs. 32 not improved for indomethacin: $p = 0.077$ in favor of ketoprofen (borderline significance).

6.3.5. Percentage of improved patients

a. Investigator's global assessment (figures in parentheses indicate percentages of marked or moderate improvement):

81.8% (43.9%) ketoprofen vs. 65.7% (34.3%) indomethacin - apparently N.S. difference.

b. Patient's global assessment (same remark as above in par. a):

68.2% (39.4%) ketoprofen vs. 52.2% (25.4%) indomethacin - apparently N.S. difference.

c. Grip strength

47.0% ketoprofen vs. 53.7% indomethacin (N.S.)

d. Duration of morning stiffness

57.6% ketoprofen vs. 56.7% indomethacin (N.S.)

6.3.6. Summary of efficacy assessment

While there were no significant interdrug differences in most of the clinical efficacy variates, there was statistically significant improvement of the functional class in favor of ketoprofen at $p < 0.05$ at weeks 1 and 12.

In addition, the most powerful measurement of rheumatic disease activity, namely, the global assessment by the investigators (references upon request - L.O.), showed statistically significant improvement ($p=0.048$) in favor of ketoprofen; similarly, the global assessment by the patients showed borderline ($p=0.077$) statistically significant improvement in favor of ketoprofen.

6.4. Safety assessment

6.4.1. Vital signs

a. Systolic BP

mean increase of 4.44 mm Hg at $p=0.02$ at week 4 for indomethacin patients: no clinical significance (L.O.).

b. Diastolic BP

mean increase of 2.29 mm Hg at $p=0.03$ at week 4 for indomethacin patients: no clinical significance (L.O.).

c. Weight

(1) Ketoprofen

mean increase of 0.91 lb. at $p=0.005$ at week 1 and of 1.03 lb at $p=0.006$ at week 2.

(2) Indomethacin

mean increase of 1.75 lb at $p < 0.001$ at week 1, of 1.70 lb at $p < 0.001$ at week 2, of 1.56 lb at $p=0.003$ at week 4, of 1.67 lb at $p=0.006$ at week 8, and of 1.82 at $p=0.005$ at week 12.

Conclusion

weight gains, obviously due to sodium and water retention, characteristic for all NSAID, occurred in the ketoprofen group significantly only during the first 2 weeks of Rx, compared to all evaluation times for the indomethacin-treated patients.

These interdrug differences were significant in favor of ketoprofen at week 1 ($p=0.038$), and of borderline significance at weeks 4 ($p=0.066$), 8 ($p=0.071$), and 12 ($p=0.076$).

6.4.2. Laboratory variates

a. Hemoglobin

Clinically possibly significant drops in Hb (i.e., 1 to 2 g%) occurred in 13/56 ketoprofen and 10/58 indomethacin pts., in addition to drops over 2 g% in 2/58 ketoprofen and 4/58 indomethacin patients; obviously, there were no statistically significant interdrug differences.

b. Hematocrit

Clinically possibly significant drops in Hct (i.e., by 5% or more) occurred in 7/56 ketoprofen and 10/58 indomethacin patients. The mean drop for the ketoprofen patients was 6.84% compared to 7.32% for the indomethacin patients.

c. BUN and creatinine

there were no significant increases from baseline of the normal values in any group; however, one elevated BUN at baseline (27 mg%), increased to 40mg% at the end of ketoprofen administration - with concomitant increase of serum creatinine from 1.1 to 1.5 mg%, resp. - but decreased from 35 mg% at baseline to 29 mg% at the end of indomethacin treatment, while the serum creatinine rose in this patient from 1.3 mg% at baseline to 1.8 mg% at the end of indomethacin Rx.

d. Urinalysis

25/70 ketoprofen and 31/70 indomethacin pts. had several abnormal findings at baseline, most of which did not become worse of the 12-week drug administration.

e. Liver function tests

subjects with abnormal baseline values - compared to the end of trial:

(1) SGOT

<u>Ketoprofen:</u>	5 abnormal baselines vs. 1 abnormal end value: 4/5 abn. baselines became normal and 1/5 remained the same at the last visit (week 12).

Indomethacin: 2 abnormal at baseline and 3 abnormal at end: 1/2 abn. baseline became slightly more elevated at week 12, while the other 1/2 became normal; one normal baseline became elevated at the end of trial.

(2) LDH

Ketoprofen: 3 abnormal baselines vs. 2 abnormal end values: 2/3 abnormal baselines became slightly more elevated while 1/3 became normalized at week 12;

indomethacin: 2 abnormal baselines vs. 2 abnormal end values: 1/2 abnormal baseline became normal at week 12, 1/2 remained abnormal; one normal became abnormal at the end of the trial.

(3) SAP

Ketoprofen: 11 abnormal baselines vs. 4 abnormal end values: 7/11 became normal at the end of the trial, 1/11 remained the same, 1/11 became slightly worse, 2/11 slightly better;

indomethacin: 14 abnormal baselines vs. 7 abnormal end values: 6/14 became normal at the end of the trial while 4/14 became worse (3/4 minimally).

(4) Total serum bilirubin

Ketoprofen: no abnormal baselines; one normal baseline (0.8 mg%) rose to 1.5 mg% after 12 weeks; this pt. had also slightly abnormal baseline SGOT and LDH which remained so throughout the treatment;

indomethacin: one abnormal baseline vs. one abnormal end value (not in the same patient), the latter having all other abnormal liver function tests at the end of the trial.

(5) Serum albumin: mean decrease of 0.53 g% in the 8 ketoprofen patients vs. 0.47 g% of the 7 indomethacin patients.

(6) Guaiac stool test: 4 positives in 3 ketoprofen pts. vs. 3 positives in 2 indomethacin patients.

6.4.2.1. Conclusion as to laboratory variates

some abnormal baselines became normal at the end of the trial, some normal (few) baselines became abnormal in both drug groups without significant interdrug differences.

6.4.3. Clinical ADR

prevalence of most frequent drug-related ADR for ketoprofen (70 pts. with a total of 322 patient-visits) vs. indomethacin (70 pts. with total 325 patient - visits):

a. Neurologic/sensory

dizziness: 1.24% vs. 1.85% at p=0.5
insomnia: 1.24% vs. 1.54% at p=0.27
headache: 6.21% vs. 9.85% at p=0.4

b. GI

dyspepsia: 5.9% vs. 3.1% at p=0.15
nausea: 1.86% vs. 2.7% at p=0.7
abd. pain: 0.93 vs. 1.54% at p=0.47.

c. Ophthalmologic examinations

Three cataracts (location, e.g., subcapsular - not specified) observed at baseline, were unchanged at the end of the ketoprofen administration.

Conclusion

no significant interdrug difference in regard to the incidence of clinical ADR.

6.4.4. Summary of safety assessment

- a. Clinically possibly significant drops of Hb and Hct occurred in both treatment groups without significant interdrug differences.
- b. No significant interdrug differences were found in regard to the incidence of clinical adverse reactions.

7. Study MDS-182: "A Double-Blind Multicenter Study to Compare the Efficacy and Safety of Ketoprofen with Ibuprofen in Rheumatoid Arthritis."

R. M. Bennett, M.D., A. Calin, M.D., A. L. Goldman, M.D., H. E. Montoya, M.D., W. M. O'Brien, M.D., F. R. Schmid, M.D., and R. F. Wilkens, M.D. administered in a randomized, double-masked and parallel design for 12 weeks either ketoprofen, initially - by 150 mg (if less than 70 Kg body weight) or 260 mg daily (if more than 70 kg), which could be adjusted to 300 mg/d or 150 mg/d (52 patients), or ibuprofen, initially 1200 mg/d or 1600 mg/d resp. which could be adjusted to 2400 mg/d or 1200 mg/day (51 patients), to a total of 103 patients, 58F, 45M, age 24-75 mean 51.1 years, with active, definite or classical R.A. of 8.4 years mean duration. There were 29/52F in the ketoprofen, and 29/51F in the ibuprofen group.

45/103 were on concomitant therapy: chrysotherapy: 16/28 ketoprofen vs. 12/28 ibuprofen pts., antimalarials: 6/12 ketoprofen vs. 6/12 ibuprofen pts., chrysotherapy and antimalarials: 2/5 ketoprofen vs. 3/5 ibuprofen patients.

7.1. Premature termination

a. Lack of efficacy

5/52 (9.6%) ketoprofen vs. 7/51 (13.7%) ibuprofen.

b. ADR

6/52 (11.5%) ketoprofen vs. 4/51 (7.8%) ibuprofen.

The dropouts in the ketoprofen group were due to dyspepsia and abdominal pain (4/6) and headache (2/6).

The dropouts in the ibuprofen group were due to nausea (2/4), nausea and vomiting (1/4), and dyspepsia with abdominal pain (1/4)

c. Other reasons

5/52 (9.6%) ketoprofen vs. 3/51 (5.9%) ibuprofen.

The five "other reasons" in the ketoprofen group were: pt. withdrew consent (2/5), Baker's cyst (1/5), not drug-related glaucoma (1/5), and lost to follow-up (1/5) (=baseline visit only).

7.2. Medication consumption and compliance

Actual drug consumption was determined by capsule count at each visit. Ketoprofen patients took a mean daily dose of 225 mg compared to 1717 mg of ibuprofen patients.

7.3. Efficacy assessment

28/103 (14 in each drug group) were excluded from efficacy analysis, mostly for "insufficient consumption of trial drug" (13/28), insufficient washout period (5/28) unauthorized aspirin intake (pos. FeCl_3 test) (5/28), etc.

The following variates comparisons are made at the last visit (as improved from baseline):

7.3.1. Functional class

ketoprofen improved from baseline at $p < 0.05$ vs. N.S. for ibuprofen - no significant interdrug difference.

7.3.2. Walking time

Ketoprofen improved from baseline at $p < 0.01$ vs. ibuprofen N.S. - also, no significant intergroup difference.

7.3.3. Mean grip strength:

both drug groups improved at $p < 0.01$ (without significant intergroup diff).

7.3.4. Morning stiffness duration:

ketoprofen improved from baseline at $p < 0.05$ vs. N.S. improvement for ibuprofen - but no significant interdrug difference.

7.3.5. Investigator's global assessment:

ketoprofen group improved from baseline at $p < 0.01$ vs. N.S. improvement for ibuprofen - but no significant interdrug difference.

7.3.6. Patient's global assessment:

same as investigator's glob. assessment in par. 7.3.5. above.

- 7.3.7. Number of tender joints (mild, mod., severe):
p < 0.001 for ketoprofen vs. < 0.05 for ibuprofen without significant interdrug difference.
- 7.3.8. Total score of tender joints (mild, mod., severe):
p < 0.001 for ketoprofen vs. < 0.01 for ibuprofen without significant interdrug difference.
- 7.3.9. Number of moderately and severely tender joints:
p < 0.001 for ketoprofen vs. p < 0.05 for ibuprofen without significant interdrug diff.
- 7.3.10. Total score of moderately and severely tender joints:
same as in par. 7.3.9. above.
- 7.3.11. Number of swollen joints (mild, mod., severe):
p < 0.01 for ketoprofen vs. p < 0.05 for ibuprofen without significant interdrug differences.
- 7.3.12. Total score of swollen joints (mild, mod., severe):
same as in par. 7.3.11. above.
- 7.3.13. Number of moderately and severely swollen joints:
same as in par. 7.3.11. and 7.3.12. above.
- 7.3.14. Total score of moderately and severely swollen joints:
same as in paragraphs 7.3.11., 7.3.12. and 7.3.13. above.
- 7.3.15. % improved patients by investigator's global assessment, N for ketoprofen =38, N for ibuprofen =37, (in parentheses are % of pts. showing moderate to marked improvement):

55.2% (23.6%) ketoprofen vs. 47.2% (16.6%) ibuprofen patients, but without significant interdrug difference.
- 7.3.16. % improved patients by patient's own global assessment:

52.6% (23.6%) ketoprofen vs. 40.5% (10.8%) ibuprofen patients without significant interdrug difference.

7.3.17. % improved grip strength patients:

50.0% ketoprofen vs. 45.9% ibuprofen patients without significant interdrug diff.

7.3.18. Morning stiffness duration:

55.2% ketoprofen vs. 51.3% ibuprofen pts.

7.3.19. Summary of efficacy assessment

While 17/18 efficacy variates showed more improvement in the ketoprofen than in the ibuprofen treated patients, none of these differences reached statistically significant (interdrug) difference.

1/8 variates improved from baseline at $p < 0.01$ for both drug products without statistically significant interdrug difference.

7.4. Safety assessment

7.4.1. Vital signs

a. Systolic BP

no statistically significant changes at any evaluation period for either drug.

b. Diastolic BP

the mean diastolic BP increased by 3.28 mm Hg at week 4 and by 5.17 at week 12 ($p=0.012$, and 0.008 resp.) in the ketoprofen group; there were no significant mean increases in the ibuprofen group.

c. Body weight

no significant mean increases in the ketoprofen group;

1.02 lb mean gain at week 1, and 1.05 lb mean gain at week 8 for ibuprofen patients ($p=0.003$, and 0.048 , resp.).

Conclusion:

- (1) Clinically nonsignificant increases of diastolic mean BP occurred for ketoprofen at week 4 and 12.
- (2) Approximately one pound mean body weight gains occurred in the ibuprofen group at week 1 and 8, apparently due to sodium - water retention.

Why did they not occur in the ketoprofen-treated group?

7.4.2. Laboratory variates - comparisons of ketoprofen vs. ibuprofen - mean changes:

a. Hemoglobin (g%)

week 1: -0.52g vs. -0.54 g;
week 4: -0.40 vs. -0.48;
week 8: -1.15 vs. -0.42 at $p < 0.05$ in favor of
ibuprofen
week 12: -0.63 vs. 0.41.

Conclusion:

statistically - but apparently not clinically - significant drop of Hb occurred at week 8 in the ketonrofen group; there were no statistically significant interdrug differences at other evaluation periods.

b. Hematocrit (%)

week 1: -0.42 vs. -0.69
week 4: -0.74 vs. -2.13
week 8: -1.06 vs. -2.47
week 12: -0.86 vs. -2.60.

Conclusion: no statistically significant interdrug differences.

c. BUN (mg %)

week 1: ibuprofen +1.02 vs. +0.57 at $p < 0.05$ in favor of
of
week 4: +1.54 vs. +1.15
week 8: +2.32 vs. +0.60
week 12: +2.54 vs. +0.74.

Conclusion: statistically - but apparently not clinically - significant elevation of the mean BUN occurred in the ketoprofen - treated patients at the end of the first week. There were no statistically significant differences of means at the remaining evaluation periods.

d. SGOT

a marginal increase in three ketoprofen and a decrease in four ibuprofen patients caused a statistically significant interdrug difference, which had no clinical relevance.

e. Hemoccult pos. blood in stool

one ketoprofen patient had positive H.-blood test at week 4, associated with decrease of Hb and Hct;

three ibuprofen patients had positive Hemoccult blood test at weeks 1, 1, and 8, resp., two of which were associated with decreases in Hb and/or Hct.

7.4.3. Clinical ADR

a. Dropouts due to ADR

6/51 ketoprofen patients dropped out due to ADR: 5/6 dyspepsia, 1/6 headache; 4/51 ibuprofen patients dropped out due to ADR: dyspepsia, nausea, dizziness, headache with N/V.

b. Total patients reporting ADR

38/51 (74.5%) ketoprofen vs. 40/51 (78.4%) ibuprofen.

c. ADR according to organ systems

(1) GI:

31/51 (60.8%) ketoprofen vs. 29/51 (56.9%).

(2) Neurologic/sensory:

18/51 (35.3%) ketoprofen vs. 25/51 (49%) ibuprofen.

(3) General:

6/51 (11.8%) vs. 6/51.

(4) Skin:

3/51 (5.9%) vs. 7/51 (13.7%).

(5) Genitourinary:

2 (3.9%) vs. 1 (2.0%).

(6) Respiratory:

0 vs. 2 (3.9%).

(7) Musculoskeletal:

0 vs. 1 (2.0%).

- d. Average proportion of moderate or severe ADR to total number of patient visits: ketoprofen vs. ibuprofen at p:
- (1) neurologic - sensory: 0.05 vs. 0.09 at p=0.3.
 - (2) cardiovascular: 0 vs. 0.
 - (3) respiratory: 0 vs. 0.
 - (4) GI: 0.22 vs. 0.19 at p=0.8.
 - (5) genitourinary: 0 vs. 0.
 - (6) Skin: 0 vs. 0.
 - (7) metabolic - endocrine: 0 vs. 0.
 - (8) musculoskeletal: 0 vs. 0.
 - (9) General: 0.01 vs. 0 at p=1.0.

Conclusion

no significant interdrug differences in regard to the incidence or severity of clinical ADR.

7.4.4. Summary of safety assessment

No clinically significant interdrug differences were observed in regard to vital signs, body weight, laboratory or clinical adverse reactions.

C. SUMMARY OF BASIS OF APPROVAL FOR RHEUMATOID ARTHRITIS

1. Adequate and Well-Controlled Studies

The approval of Orudis (ketoprofen) for the indication of rheumatoid arthritis is based on the following seven, adequate and well-controlled studies:

- a. Randomized, double-masked and parallel 6-week study of 284 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom fourteen competent and independent clinical investigators, utilizing identical protocol, administered either ketoprofen (Orudis) at 200 mg per day as 50 mg q.i.d. (97 patients), or at 300 mg per day as 75 mg q.i.d. (93 patients), or placebo (94 patients).

In 10 out of 14 clinical efficacy variates, ketoprofen was definitely statistically superior to placebo, however, without complete dose proportionality. In the remaining four clinical efficacy variates, no statistically significant differences were found between both ketoprofen dosages and placebo.

In regard to safety, there were surprisingly no statistically significant differences between both doses of ketoprofen and placebo in the number of patients reporting one or more clinical adverse drug reactions as well as in the number of patients experiencing specific organ system adverse reactions (cf. par. IV. B. 1. above).

- b. Randomized, double-masked and parallel 6-week study of 106 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom eight competent and independent clinical investigators, utilizing identical protocol, administered either ketoprofen (Orudis), 300 mg per day as 150 mg b.i.d. (65 patients), or placebo b.i.d. (41 patients); the dosage of ketoprofen was to be increased to 400 mg per day (200 mg b.i.d.), if the initial response was judged to be inadequate.

In 7 out of 8 (analysis of covariance) and in 6 out of 6 (Kruskal-Wallis test), ketoprofen (Orudis) was definitely statistically superior to placebo.

Some statistically - but no clinically - significant intergroup differences in favor of placebo occurred in several laboratory tests.

There were no statistically significant difference between ketoprofen (Orudis) and placebo in regard to the incidence of adverse reactions related to specific organ systems as well as to the incidence of dropouts due to clinical adverse reactions (cf. par. IV.B.2. above).

- c. Randomized, double-masked and parallel 24-week study of 145 patients with adult - onset, active, definite or classical rheumatoid arthritis to whom eight competent and independent clinical investigators, utilizing identical protocol, administered either ketoprofen (Orudis) at a mean daily dose of 216.2 mg, given as a q.i.d. dosage (71 patients, or placebo q.i.d. (74 patients). All patients were maintained on corticosteroid therapy, not exceeding the equivalent of 15 mg prednisone per day. They were further stratified to functional class 1 and 2 (total of 58 analyzable patients, 27/58 in the ketoprofen group) and functional class 3 and 4 (total of 34 analyzable patients, 16/34 in the ketoprofen group).

The more severely ill patients (class 3 and 4) improved statistically significantly more in the ketoprofen treated group than in the placebo-treated group, both, at the average and at the last (i.e., week 24) visit.

In regard to safety, with the exception of statistically significant higher incidence of dyspepsia in the ketoprofen group, and of diarrhea in the placebo (sic!) group, there were no significant intergroup differences as to the incidence of laboratory or clinical adverse drug reactions (cf. par. IV.B.3. above).

- d. Randomized, double-masked and parallel 54-week (fifty-four week) study of 229 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom nine competent and independent clinical investigators, utilizing identical protocol, administered either ketoprofen (Orudis) at a mean daily dose of 246.4 mg given as a q.i.d. dosage (115 patients), or aspirin at a mean daily dosage of 4.03 g, also given as a q.i.d. dosage (114 patients). There were at baseline statistically significantly more severely ill patients in the ketoprofen-treated than in the aspirin-treated group (46 vs. 31 at $p = 0.05$); not unexpectedly, the former also received significantly more concomitant long-acting antirheumatic agents like gold salts or antimalarials.

All twelve efficacy variates improved from baseline very significantly at all five evaluation periods for both drugs (with the exception of the functional class for ketoprofen at week 54), and, with the exception of patients own assessments at week 4 and at the last visit (in favor of aspirin), there were no statistically significant interdrug differences in the remaining 166 out of 168 variates x periods.

In regard to safety, seven (out of twenty-six) adverse drug reactions occurred statistically significantly more frequently in the aspirin-treated patients while there were no significant intergroup differences in the incidence of the remaining 19 clinical adverse drug reactions. No consistent, clinically important trend was found in the laboratory tests values (cf. par. IV.B.4. above).

- e. Randomized, double-masked and parallel 24-week study of 81 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom five competent and independent clinical investigators, utilizing identical protocol administered either ketoprofen (Orudis) at a mean daily dose of 247.3 mg, given as a q.i.d. dosage (41 patients), or aspirin at a mean daily dose of 3.805 g, also given as a q.i.d. dosage (40 patients). The majority of patients in each group were maintained on chrysotherapy and/or antimalarials and corticosteroids.

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All ten clinical efficacy variates improved statistically significantly, from baseline at the last (24th) week for both drugs without significant interdrug differences.

Some statistically - but not clinically - significant drops of hemoglobin and hematocrit occurred in both drug groups without significant interdrug differences. With the exception of the significantly higher incidence of tinnitus (and possibly dyspepsia) in the aspirin-treated patients; there were no statistically significant interdrug differences in regard to clinical adverse reactions (cf. par. IV.B.5. above).

- f. Randomized, double-masked and parallel 12-week study of 140 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom seven competent and independent clinical investigators, utilizing identical protocol administered either ketoprofen (Orudis) at a mean daily dose of 223 mg, given as a q.i.d. dosage (70 patients), or indomethacin at a mean daily dose of 113 mg, also given as a q.i.d. dosage (70 patients).

While there were no significant interdrug differences in most of the clinical efficacy variates, there was statistically significant improvement of the functional class in favor of ketoprofen at weeks 1 and 12. Furthermore, the most powerful measurement of rheumatic disease activity, namely, the global assessment by the investigator, also showed statistically significant improvement in favor of ketoprofen.

In regard to the safety, clinically possibly significant drops in hemoglobin and hematocrit values occurred in both treatment groups without significant interdrug differences; in addition, no significant interdrug differences were found in regard to the incidence of clinical adverse drug reactions (cf. par. IV.B.6. above).

- g. Randomized, double-masked and parallel 12-week study of 103 patients with adult-onset, active, definite or classical rheumatoid arthritis to whom seven competent and independent clinical investigators, utilizing identical protocol, administered either ketoprofen (Orudis) at a mean daily dose of 225 mg (52 patients), or ibuprofen at a mean daily dose of 1717 mg (51 patients), both given on a t.i.d. (lower dose) or q.i.d. (higher dose) basis. Almost one-half of the patients were on concomitant stable antimalarial and/or chrysotherapy.

While seventeen out of eighteen clinical efficacy variates showed more improvement from baseline in the ketoprofen - than in the ibuprofen - treated patients, none of these interdrug differences reached statistical significance.

In regard to safety, no clinically significant interdrug differences were observed in the prevalence or severity of laboratory or clinical adverse drug reactions.

C.2. CONCLUSIONS OF S.B.A. FOR R.A.

Out of seven adequate and well-controlled clinical studies of 1088 patients afflicted with adult-onset, active, definite or classical rheumatoid arthritis, three studies, encompassing 535 patients, demonstrated significant superiority of ketoprofen over placebo in alleviation of signs and symptoms of this disease, two (310 patients) its therapeutic equivalence to aspirin, one (140 patients) its therapeutic equivalence to indomethacin, and one (103 patients) to ibuprofen.

In regard to safety, there were surprisingly no statistically significant differences (with the exception of more frequent dyspepsia in the placebo-treated group in one study) in the prevalence of clinical adverse drug reactions in any of the three placebo-controlled studies, while several clinical side effects occurred significantly more frequently in the two aspirin-controlled studies, and with about the same prevalence in the indomethacin and in the ibuprofen controlled studies.

D. OSTEOARTHRITIS

1. Study MDS - 228A: "A Double-Blind Parallel Comparative Evaluation of the Efficacy and Safety of Ketoprofen versus Placebo in the Treatment of Osteoarthritis."

R. D. Brobyn, M.D., J. S. Johnson, M.D., J. I. McMillen, M.D., A. Miyara, M.D., and J. E. Poilley, M.D. administered in a randomized, double-masked and parallel design for 4 weeks to 99 patients with osteoarthritis of the hip and/or knee, confirmed by radiologic evidence and clinical findings, 57F, 42M, age 40-87, mean 64 years, with duration of the disease from 0.2 to 36.2, mean 9 years, 31/99 with coxarthrosis and 68/99 with gonarthrosis, who were given either 50 mg q.i.d. of ketoprofen (32 pts.), or 75 mg q.i.d. of ketoprofen (32 pts.), or placebo q.i.d. (35 pts.).

The patients were evaluated at baseline and at weekly intervals.

1.1 Concomitant therapy

All oral and intraarticular concomitant medications for musculoskeletal disorders were to be discontinued for the duration of the study, including nonprescription products containing salicylates.

1.2. Premature termination

a. Lack of efficacy:

5/32 ketoprofen 200 mg vs/ 0/32 ketoprofen 300 mg vs. 9/35 placebo = statistically significant in favor of ketoprofen 300 mg dose.

b. Clinical adverse reactions:

1/32 ketoprofen 200 mg (dyspepsia) vs. 2/32 ketoprofen 300 mg (dyspepsia; insomnia with mild epigastric pain) vs. 2/35 placebo [peptic ulcer (sic!); abdominal pain].

c. Other reasons:

3 patients (1/3 from each Rx) dropped out for lack of cooperation and misdiagnosis.

1.3. Medication consumption and compliance

The 200 mg-ketoprofen patients took a mean of 182.4 mg/day, the 300 mg-ketoprofen patients a mean of 287.4 mg/day, and the placebo patients a mean of 3.8 capsules a day. If a patient took less than 75% of the prescribed dose, he/she was excluded from efficacy analysis for this visit.

10/99 patients were excluded from efficacy analysis: 2/10 ketoprofen 200 mg/d pts., 3/10 ketoprofen 300 mg/d, and 5/10 placebo pts. The reasons for the exclusions were: 2/10 misdiagnosed (as R.A.), 4/10 did not fully comply with the dosage, 4/10 violated protocol (took salicylates concomitantly).

1.4. Comparison of treatment groups at baseline:

The groups were statistically comparable except in walking time where patients in the 300 mg/day ketoprofen group had a slightly higher baseline mean value (22.9 sec) vs. 19.7 sec of the 200 mg/day ketoprofen vs. 17.7 sec of the placebo group ($p=0.036$); while three statistically significant differences between the "joint involvement" subpopulation (coxarthrosis vs. gonarthrosis pts.) were observed at baseline, there was no statistically significant interaction observed between joint involvement and treatment.

1.5. Validation of data pooling

Significant investigator x treatment interaction was only seen in walking time (week 3, the average and last visit analysis), and in global assessment at week 1 only.

1.6 Efficacy assessments of ANACOVA

1.6.1. Investigator's global assessment

a. Ketoprofen 200 mg/day

23/32 (72%) improved vs. 9/32 (28%) not improved at $p < 0.01$;

b. ketoprofen 300 mg/day

same as above;

c. placebo:

18/35 (51%) improved vs. 17/35 (49%) not improved (N.S.).

1.6.2. Patient's own global assessment

a. ketoprofen 200 mg/day

23/32 (72%) improved vs. 9/32 (28%) not improved at $p < 0.01$;

b. ketoprofen 300 mg/day

25/32 (78%) improved vs. 7/32 (22%) not improved at $p < 0.001$;

c. placebo:

16/35 (46%) improved vs. 19/35 (54%) not improved (N.S.).

1.6.3. Walking time

Improved for either or both ketoprofen dose levels over placebo at $p = 0.001$ (ANACOVA) at all six evaluation periods, i.e., 1, 2, 3, 4 weeks, average visit (average response over all follow-up visits), and last visit (final actual evaluation).

1.6.4. Morning stiffness duration

Improved for either or both ketoprofen dose levels over placebo at $p < 0.001$ at week 1 and at average visit, and at last visit at $p < 0.009$; N.S. for all other visits.

N.B.: Morning stiffness is a discriminating variate for rheumatoid arthritis, not for osteoarthritis (L.O.).

1.6.5. Morning pain

Improved for either or both ketoprofen dose levels over placebo at $p < 0.001$ at week 1, at $p < 0.05$ at weeks 2 and 3, and at $p < 0.01$ at average visit; N.S. at week 4 and last visit.

1.6.6. Night pain

N.S. at any evaluation period.

1.6.7. Walking pain

Improved for either or both ketoprofen dose levels over placebo at $p < 0.001$ at week 3 and at average visit, at $p < 0.01$ at weeks 1 and 4 and at last visit, at $p < 0.05$ at week 2.

1.6.8. Pain index

Improved for either or both ketoprofen dose levels over placebo at $p < 0.001$ at week 1 and at average visit, at $p < 0.01$ at week 3, at $p < 0.05$ at week 2 and at last visit; N.S. at week 4.

1.6.9. Swelling index

Improved for either or both ketoprofen dose levels over placebo at $p < 0.001$ at week 1, at $p < 0.01$ at average visit at $p < 0.05$ at weeks 2 and 3; N.S. at week 4 and at last visit.

1.6.10. SUMMARY OF ANACOVA (1.6.3. - 1.6.9.):

With the exception of night pain (which variate should be used more appropriately in spondylarthropathies, than in arthroses - L.O.), in the remaining six clinical efficacy variates, ketoprofen at either or both dose levels proved to be significantly more efficacious than placebo at the vast majority of evaluation points in relieving the signs and symptoms of cox- and/or gonarthrosis.

1.7. Efficacy assessments of KRUSKAL-WALLIS test

N.B.: The K-W test is a non-parametric, i.e., distribution - free test (L.O.), and all 99 patients are involved in the following results, pertaining to the average response and final evaluation:

- a. walking time: N.S. for both drugs;
- b. morning stiffness duration:
improvement at $p=0.026$ at average response, and at $p=0.02$ at final evaluation for both, low and high doses of ketoprofen - as compared to placebo;
- c. morning pain:
 $p=0.009$ and $p=0.029$, resp., for high ketoprofen dose, only;
- d. night pain:
 $p=0.008$ and $p=0.025$, resp., the former for both, the latter for high ketoprofen dose, only;
- e. walking pain:
 $p=0.013$ and $p=0.012$ resp., the former for both, the latter for high ketoprofen dose, only;
- f. pain index:
N.S. for both drugs;
- g. swelling index: same as in par. f.;
- h. investigator's global assessment:
 $p=0.001$ for both doses, and $p=0.007$ for low (!) dose of ketoprofen only;
- i. patient's global assessment:
 $p < 0.001$ and $p=0.004$ for both doses of ketoprofen.

1.7.1. Summary of KRUSKAL - WALLIS (nonparametric) test:

In the two most powerful discriminatory variates of rheumatic activity, namely the investigator's and patient's own global assessment, the efficacy of both ketoprofen doses was highly significantly superior to that of placebo.

1.8. Safety assessment

1.8.1. Vital signs

except for a mean weight increase of 3.23 lb in 8 ketoprofen - treated patients (6/8 in the . gh, 2/6 in the low dose), there were no statistically or clinically significant changes in body weight, pulse rate, syst. and diast. blood pressure.

1.8.2. Laboratory tests

a. BUN:

statistically - but not clinically - significant of +2.93 mg% mean change from baseline was observed in the 200 mg/day ketoprofen, and of +2.81 mg% in the 300 mg/day dose.

b. Total protein:

-0.22 g% mean change from baseline for the 200 mg/day dose of ketoprofen (clinically insignificant).

c. Serum globulin:

-0.18 g% mean change from baseline for the 200 mg/d ketoprofen dose, and -0.16 g% for the 300 mg/d dose (clinically insignificant).

d. SUA:

-0.50 mg% mean change from baseline for the 300 mg/day dose of ketoprofen (clinically insignificant - L.O.).

e. Occult blood in stool:

positive Hemocult tests were found in 3/32 200 mg/d ketoprofen patients having 3/148 (2.03%) positive findings, in 2/32 300 mg/d ketoprofen patients having 2/152 (1/32%) positive findings and in 1/35 placebo patient with 1/145 (0.7%) positive finding.

N.B.: the above mentioned (par. a.) increases in BUN were not accompanied by increases in serum creatinine or by decreases in total serum protein except in one patient.

Conclusion:

no clinically significant changes in laboratory tests were found in this 4-week study.

1.8.3. Clinical ADR

a. Neurologic/sensory:

moderate to severe ADR occurred in 2/32 200 mg ketoprofen, 3/32 300 mg ketoprofen, and 1/35 placebo patient (N.S.).

b. GI:

moderate to severe ADR occurred in 2/32 200 mg ketoprofen, 4/32 300 mg ketoprofen, and 2/35 placebo patients (N.S.).

c. Skin:

moderate to severe ADR occurred in 0/62 ketoprofen and 1/35 placebo pt. (N.S.).

d. No patient reported any cardiovascular, respiratory, genitourinary, metabolic/endocrine or musculoskeletal ADR.

Conclusion:

no statistically significant interdrug differences in incidence of moderate to severe clinical adverse reactions.

2. Study MDS - 289A: "A Double-Blind, Parallel Comparative Evaluation of the Efficacy and Safety of Ketoprofen versus ASA in the Treatment of Osteoarthritis."

H. M. Adelman, M.D., R. D. Brobyn, M.D., J. R. Calwell, M.D., J. I. McMillen, M.D., and E. L. Tarpley, M.D. administered for 12 weeks in a randomized, double-masked and parallel design to 85 patients with gonarthrosis (45/85 pts.), or coxarthrosis (40/85 pts.), 58F, 27M, age 35-83, mean 62.9 years, with duration of the disease from 0.8-45.1, mean 9.7 years, either ketoprofen, 50 mg q.i.d., mean 190 mg/day, or aspirin, 650 mg q.i.d., mean 2364 mg/day; the patients were evaluated for efficacy at baseline, and at weeks 1, 2, 4, 8, and 12.

2.1. Concomitant therapy:

same as in par. D.1.1. above.

2.2. Premature termination

a. Lack of efficacy:

8/42 (19.1%) ketoprofen vs. 5/43 (11.6%) aspirin patients.

b. Clinical ADR:

2/42 (4.8%) ketoprofen (peptic ulcer, and diarrhea with abdominal pain) vs. 4/43 (9.3%) aspirin patients (2/4 dyspepsia; petechial rash, and epigastric pain).

c. Uncooperative patients and wrong diagnosis

0 ketoprofen vs. 2/43 aspirin patients.

Conclusion: no statistically significant interdrug differences.

2.3. Medication consumption and compliance

If a patient took less than 80% of the prescribed daily dose, that treatment period was excluded from efficacy analysis. A total of 20 patient visits (7/20 ketoprofen, 13/20 aspirin) were excluded from the statistical analysis for noncompliance; also, three patients, 1/3 ketoprofen, 2/3 aspirin, were fully excluded for this reason.

2.4. Efficacy assessments

a. Interdrug analyses

With the exception of statistically significant superiority of ketoprofen over aspirin at both the final visit and week 12 in controlling pain and walking pain, there were no statistically significant interdrug differences in the remaining seven clinical efficacy variates (duration of morning stiffness, pain index, swelling index, global assessments by investigator and by patient, et al.).

In addition, in the gonarthrosis group ketoprofen showed significantly greater improvement in walking time than aspirin at week 12.

b. Intradrug analyses

(1) Ketoprofen:

significant improvement observed in 59/63 clinical efficacy variates/periods while 4/63 showed no significant improvement: global assessment by the investigator and by the patient, both at weeks 1 and 2.

(2) Aspirin:

significant improvement observed in 56/63 clinical efficacy variates/periods while 7/63 showed no significant improvement: 4/7 the same as for ketoprofen in par. (1) above, plus global assessment by investigator at week 8, and walking time at week 12 and at last visit.

c. Overall therapeutic response (OTR)

(1) OTR rated by investigator

- (a) ketoprofen: 28/42 (66.7%) improved vs. 14/42 not improved at $p < 0.05$;
- (b) aspirin: 27/43 (62.8%) improved vs. 16/43 not improved (N.S....);

(2) OTR rated by patient

- (a) ketoprofen: 30/42 (71.4%) improved vs. 12/42 not improved at $p < 0.01$;
- (b) aspirin: 29/43 (67.4%) improved vs. 14/43 not improved at $p < 0.05$;

Conclusion: somewhat marginally better performance of ketoprofen, although without statistically significant interdrug differences.

d. Marked improvement

- (1) by investigator: 14/42 ketoprofen vs. 9/43 aspirin;
- (2) by patient: 15/42 ketoprofen vs. 10/43 aspirin.

e. Worsening

- (1) by investigator: 4/42 ketoprofen vs. 7/43 aspirin;
- (2) by patient: 5/42 ketoprofen vs. 7/43 aspirin.

Conclusion: (for par. d. and e.): no statistically significant interdrug differences.

f. Supplementary efficacy analysis: all patients

All data excluded from the above described analyses for protocol violations were included in this suppl. analysis with the results almost identical with those obtained in the efficacy-analyzable sample; ketoprofen was found to be significantly superior to aspirin in affecting the walking pain at final visit and average response, and morning pain (final visit only).

2.5. Safety assessment

2.5.1. Vital signs and body weight

- a. A statistically significant decrease in syst. BP was seen for the aspirin group at weeks 1, 2, 8, and 12, while no significant syst. BP were observed in the ketoprofen patients.
- b. Two investigators reported a mean change of +1.7 and +3.63 lb., resp. in the ketoprofen group, and three investigators a mean change of +1.2, +1.2, and +3.25 lb. in the aspirin group.

2.5.2. Laboratory data

a. Ketoprofen:

Hct, decrease by 1.74%;
Hb decrease by 0.47g%;
BUN increase by 1.79 mg%;
WBC decrease by 670/mm³;
tot. plasma protein decrease by 0.36g%;
serum globulin decrease by 0.23g%;
neutrophils decrease by 589/mm³.

b. Aspirin:

WBC decrease by 460/mm³;
tot. plasma protein decrease by 0.26g%;
SUA decrease by 0.53mg%;
globulin decrease by 0.24g%;
neutrophils decrease by 391/mm³.

c. Occult blood in stool (Hemoccult):

5/42 pts. with positive findings in the ketoprofen vs. 1/43 in the aspirin group at p=0.1. 7/29 positive tests in the ketoprofen vs. 2/186 in the aspirin group at p=0.1.

2.5.3. Clinical ADR

a. Number of patients reporting one or more ADR:

12/42 (28.6%) ketoprofen vs. 14/43 (32.6%) aspirin.

b. # of dropouts due to ADR:

2/42 (4.8%) ketoprofen (peptic ulcer; diarrhea with abdominal pain) vs. 4/43 (9.3%) aspirin (2/4 dyspepsia; petechial rash; epigastric pain - see also 2.2.b. above).

c. ADR according to organ systems

- (1) Neurologic/sensory: 2/42 ketoprofen vs. 2/43 aspirin.
- (2) Cardiovascular: 2/42 ketoprofen vs. 0/43 aspirin.
- (3) GI: 10/42 (23.8%) ketoprofen vs. 11/43 (25.6%) aspirin.
- (4) GU: 1/43 ketoprofen vs. 0/43 aspirin.
- (5) Skin: 0/42 ketoprofen vs. 1/43 aspirin.
- (6) Musculoskeletal: 0/42 ketoprofen vs. 1/43 aspirin.
- (7) General: 0/42 ketoprofen vs. 1/43 aspirin.

From the more frequent ADR, flatulence occurred significantly more often in the ketoprofen group, and dyspepsia in the aspirin group.

2.5.4. Summary of safety assessment:

With the exception of flatulence in the ketoprofen - treated and dyspepsia in the aspirin patients, there were no statistically significant interdrug differences in the prevalence of clinical ADR, or of clinically significant interdrug variations in the laboratory test parameters.

3. Study MDS - 275A: "A Single-Blind Multicenter Dose-Titration Study of Ketoprofen in Osteoarthritis."

M. Albert, M.D., M. L. Brandon, M.D., and P. D. Vreede, M.D. administered ketoprofen in a single-masked and parallel design to 60 patients with cox- (32/60 pts.) or gonarthrosis (28/60 pts.), 41F, 19M, age 40-84, mean 64 years, with duration of the disease from 1-37, mean 9.5 years, for a total of 3 weeks as follows: 25 mg q.i.d. (mean 96.7 mg/day) during the first week, 50 mg q.i.d. (mean 195.7 mg/day) during the second week, and 75 mg q.i.d. (mean 285.5 mg/day) during the third week. 58/60 pts. (39F, 19M) had the dosage increased to 300 mg/day of ketoprofen at 200 mg/day, and another 1/60 decreased to 100 mg/day due to ADR. The patients were evaluated at weekly intervals.

3.1. Concomitant therapy

Concurrent medications were continued during the study, the most frequent (24/60) being hydrochlorothiazide, given for hypertension.

3.2. Efficacy assessments

3.2.1. Exclusions from efficacy analysis:

7/60 patients were excluded from the efficacy analysis for the following reasons:

1/7 Paget's disease;
1/7 positive urine salicylate at baseline washout;
5/7 non-compliance.

3.2.2. Main efficacy variates

a. Investigator's global assessment

(1) individual investigators:

2/3 investigators (Albert, Brandon) reported improvement at the third (last) week at $p < 0.001$ as compared to baseline, while 1/3 investigator (Vreede) reported improvement from baseline thru week 3 at $p=0.025$;

(2) all three investigators:

improvement from baseline at week 3 at $p < 0.001$.

b. Patient's own global assessment

same as in par. (1) and (2) above.

3.2.3. Summary of efficacy assessments

Both, investigators' and patients' own global assessments, reflected improvement from baseline at the third (last) week at $p < 0.001$.

3.3. Safety assessments

3.3.1. Body weight

mean increases of body weight were observed by 1.12 lb at week 1, by 0.83 lb. at week 2, and by 0.48 lb. at week 3, all statistically - but not clinically - significant.

3.3.2. Vital signs

A mean decrease of diastolic BP of -2.35 mm Hg was observed at week 3 (while statistically significant at $p < 0.01$, this is obviously clinically insignificant). Systolic BP and pulse rate did not show any statistically significant changes at week 3.

3.3.3. Laboratory tests

Statistically - but not clinically - significant mean changes occurred in the following variates:

- a. Neutrophils: decrease by $-420/\text{mm}^3$ and $+460/\text{mm}^3$, resp., in week 2 and 3 resp.
- b. Lymphocytes: increases by $+160/\text{mm}^3$ and $+140/\text{mm}^3$, resp., in week 2 and 3 resp.
- c. BUN: mean increases by $+1.6 \text{ mg\%}$, $+2.6 \text{ mg\%}$, and $+2.4 \text{ mg\%}$, resp., at weeks 1, 2, and 3, resp.

N.B.: these slight BUN increases may be well attributed to the prostaglandin inhibition and the resulting renal hemodynamics, common to the NSAIDs. In one initially abnormal ($36 \text{ mg\%}$) case, the BUN was elevated to $47 \text{ mg\%}$ after the...placebo week, and was not determined thereafter.

- d. Serum globulin: mean decreases by $-0.13 \text{ g\%}$, $-0.16 \text{ g\%}$, and $-0.22 \text{ g\%}$, resp., at weeks 1, 2, and 3 resp.
- e. Total protein: mean decreases by $-0.21 \text{ g\%}$, $-0.24 \text{ g\%}$, and $-0.25 \text{ g\%}$, resp., at weeks 1, 2, and 3, resp.

3.3.4. Clinical ADR

- a. Number of patients reporting one or more ADR

6/60 placebo - 3/60 ketoprofen 100 mg/day - 10/60
ketoprofen 200 mg/day - 6/60 ketoprofen 300 mg/d.

Remark: the number of clinical adverse reactions on the maximum dose of ketoprofen was identical to the number (of patients reporting) ADR during the initial placebo washout week.

- b. ADR according to organ systems

- (1) Neurologic/sensory: 1/60 (1.7%)
- (2) Cardiovascular: 1/60 (1.7%)
- (3) GI: 7/60 (11.7%)*
- (4) genitourinary: 1/60 (1.7%)
- (5) skin: 1/60 (1.7%)
- (6) general: 5/60 (8.3%).

* Mostly dry mouth and flatulence. In addition, peripheral edema occurred in 3/60 patients (NSAID common side-effect).

c. EKG: no abnormalities as compared to baseline.

d. Audiograms:

no abnormalities except in one pt. (Dr. Vreede, #18), who had a minimal loss of low frequency hearing in the left ear at the end of week 3.

N.B.: one pt. had tinnitus at baseline only (indication of previous aspirin ingestion), whereas the tinnitus disappeared during ketoprofen treatment.

3.3.5. Summary of safety assessments

- a. No clinically significant changes occurred in regard to vital signs and laboratory tests.
- b. The most common clinical ADRs were gastrointestinal (7/60 = 11.7%), particularly dry mouth and flatulence.

E. SUMMARY OF BASIS OF APPROVAL FOR OSTEOARTHRITIS

1. Adequate and Well-Controlled Studies

The approval of Orudis (ketoprofen) for the indication of osteoarthritis is based on the following two adequate and well-controlled studies:

- a. Randomized, double-masked and parallel 4-week study of 99 patients with osteoarthritis of the hip (31 patients) and of the knee (68 patients) to whom five competent and independent clinical investigators, utilizing identical protocol administered either ketoprofen (Orudis) at 200 mg per day as 50 mg q.i.d. (32 patients), or ketoprofen at 300 mg per day as 75 mg q.i.d. (32 patients), or placebo q.i.d. (35 patients).

As judged by ANACOVA, with the exception of night pain (which variate should be used more appropriately in spondylarthropathies, than in arthroses - L.O.), in the remaining six clinical efficacy variates, ketoprofen at either or both dose levels proved to be significantly more efficacious than placebo at the vast majority of evaluation points in relieving symptoms of cox- and/or gonarthrosis.

As judged by the (nonparametric = distribution-free) Krushal-Wallis test, in the two most powerful discriminatory variates of rheumatic activity, namely, the investigator's and the patient's own global assessments, the efficacy of both ketoprofen dose levels was highly significantly superior to that of placebo.

- b. Randomized, double-masked and parallel 12-week study of 85 patients with osteoarthritis of the hip (40 patients) and of the knee (45 patients) to whom five competent and independent investigators, utilizing identical protocol, administered either ketoprofen (Orudis) at 200 mg per day as 50 mg q.i.d. (42 patients), or aspirin, 2600 mg per day as 650 mg q.i.d. (43 patients).

As judged by ANACOVA, with the exception of the statistically significant superiority of ketoprofen over aspirin at both, the final visit and week 12, in controlling pain and walking pain, there were no statistically significant interdrug differences in the remaining seven clinical efficacy variates.

In regard to safety - with the exception of flatulence in the ketoprofen-treated and dyspepsia in the aspirin-treated patients - there were no statistically significant interdrug differences in the prevalence of clinical adverse reactions or of clinically significant interdrug variations in the laboratory test parameters.

2. Supportive study

Randomized, single-masked and parallel 3-week study of 60 patients with osteoarthritis of the hip (32 patients) and of the knee (28 patients) to whom three competent and independent clinical investigators, utilizing identical protocol administered ketoprofen, 25 mg q.i.d. during the first week, 50 mg q.i.d. during the second week, and 75 mg q.i.d. during the third week.

Both, investigators' and patients' own global assessments reflected highly significant improvement from baseline at the third (last) week.

In regard to safety, the most common clinical adverse reactions were gastrointestinal (11.7%), particularly dry mouth and flatulence.

E.2. CONCLUSIONS OF S.B.A. FOR O.A.:

Two adequate and well-controlled studies of 4- and 12-week duration, resp., encompassing 184 patients with osteoarthritis of the hip (71 patients) and the knee (113 patients), demonstrated significant superiority of ketoprofen over placebo, as well as the therapeutic equivalence of ketoprofen to ibuprofen, in relieving symptoms of this disease.

In regard to safety, there were no clinically significant differences between ketoprofen and placebo, or ketoprofen and ibuprofen.

A 3-week supportive study of 60 patients with osteoarthritis of hip (32 patients) and of the knee (28 patients) confirmed the efficacy and safety of ketoprofen in the treatment of this disease.

J. SUPPORTIVE STUDIES

1. Rheumatoid arthritis

- a. Study MSD-189: "A Double-Blind Multicenter Comparative Study of Ketoprofen vs. Placebo in Rheumatoid Arthritis." G. B. Bluhm, M.D., S. Roth, M.D. and R. A. Turner, M.D. administered in a randomized, double-masked and parallel design for 24 weeks either ketoprofen, initially 50 mg t.i.d. which could be increased to 200 or 250 mg/day, to 52 patients with active, definite or classical R. A., 37F, 15M, age 28-81, mean 53.7 years, with duration of the disease from 1 to 43, mean 12.8 years, or placebo to 53 patients, 40F, 13M, age 24-77, mean 53.3 years, with the duration of the disease from 1-32, mean 9.2 years.

(1) Efficacy assessment

The trial design was not adequate for a reliable efficacy assessment because of the allowed intake of aspirin at therapeutic doses (up to 3.6 g per day), which was intended as rescue drug but used primarily as a preventive medication... However, the consumption of aspirin was statistically significantly lower ($p=0.007$) in the ketoprofen-treated patients than in the placebo group. The efficacy data were not analyzed.

(2) Safety assessment

(a) ADR according to organ systems

neurologic/sensory: 27/52 ketoprofen vs. 24/52 placebo;

GI: 21/52 ketoprofen vs. 23/52 placebo;

Skin: 10/52 ketoprofen vs. 8/52 placebo;

General: 6/52 ketoprofen vs. 5/52 placebo;

Genitourinary: 1/52 ketoprofen vs. 3/52 placebo.

Remarks: the prevalence of clinical ADR was obscured by the fact that both groups took aspirin; the mean aspirin consumption was 5.03 tablets/day (=2250 mg/day) in the placebo group.

Conclusion: under the conditions of this trial, it was impossible to assess the absolute or relative safety and efficacy of ketoprofen.

- b. Study MDS-189A: "A Long-Term Safety Study of Ketoprofen in Rheumatoid Arthritis." G. B. Bluhm, M.D., S. Roth, M.D., and R. A. Turner, M.D.

84 patients of the 105 patients described in par. J.1.a.

immediately above, entered the open-label phase of the study, lasting for up to 3 years. The open-label treatment was maintained for a mean of 404 days; 21/84 patients (25%) had open-label treatment longer than 1000 days; 22/84 patients remained in the study until its termination with the exposure to ketoprofen for 546-1137, mean 1174 days.

(1) Premature termination

(a) Before one year:

29/84 dropped out because of inefficacy. 10/84 dropped out because of the following ADR: 4/10 abdominal discomfort, 2/10 nausea and/or vomiting, 1/10 headache, 1/10 PMVC (premature ventricular contractions), 1/10 anorexia, and 1/10 blurred vision; 11/84 for other reasons, incl. moving out of state, etc.

(b) After one year:

3/84 dropped out because of inefficacy. 2/84 dropped out because of adverse reactions (elevated hepatic enzymes; abdominal pain). 29/84 for other reasons, incl. 24/29 termination at the request of the sponsor - as planned for 1979.

(2) Drug consumption

mean of 258.0 mg ketoprofen per day.

(3) Efficacy assessment:

omitted because there was no control group to which compare efficacy in the open-label phase.

As shown above [par. (1)], 32/84 (38%) patients were withdrawn from the study for lack of efficacy, mostly within the first year of treatment. Of the 22/84 who were in the study at its termination, 15/22 had their global condition rated as "very good" or "good" by the investigator, and 16/22 had these ratings by their own assessment.

(4) Safety assessment

N.B.: additional ten patients from the double-masked phase were followed up here, making a total of 94 patients.

(a) Vital signs and body weight

two diastolic BP decreases of borderline statistical significance, but clinically irrelevant.

(b) Laboratory tests

(b.1.) Lymphocytes:

mean decreases from 157 to 461/mm³ at 4 (monthly) visits.

(b.2.) Hemoglobin:

mean decreases from 0.23 to 0.50g% at 7 (monthly) visits.

(b.3.) BUN:

mean increases from 1.10 to 1.77 mg% at 9 (monthly) visits.

(b.4.) Serum total bilirubin:

mean increases from 0.07 to 0.18 mg% at 8 (monthly) visits.

(b.5.) Serum total protein:

mean decrease of 0.16 g% at 3 (monthly) visits.

Conclusion:

none of these mean laboratory test changes was clinically significant.

(b.a.) Clinically relevant laboratory test changes

Hemoglobin:

6/94 patients had clinically relevant decreases of hemoglobin:

- (1) from 13.4 g% at baseline to 10.7 g% at the end of the 3-year administration;
- (2) from 13.1 g% to 11.0 g%;
- (3) from 12.5 g% to 10.7 g% at the end of Rx;
- (4) from 12.6 g% to 10.8 g%;
- (5) from 13.9 g% to 11.6 g% after one year of treatment;
- (6) from 14.8 g% at baseline to 12.6 g% after 1 1/2 years of treatment.

N.B.: with the exception of an isolated Hemocult test, no

Leukopenia (1/94):

drop from 5,200 WBC/mm³ at baseline to 2,400/mm³ after 4 months of Rx.

N.B.: this patient had a history of WBC decrease with two other investigational NSAIDs; one year later, the WBC were 4,000/mm³.

BUN (2/94):

- (1) increase from baseline 25 mg% (upper limits of normal) to 36 mg% after 3 1/2 years of ketoprofen;
- (2) increase from baseline 26 mg% to 39 mg% one month later, and decrease to 34 mg% at termination of the 3-year ketoprofen administration.

Transaminases (1/94):

increase from unknown baseline of SGOT to 28 ($N \leq 26U$) and SGPT to 50 ($N \leq 23$) after 16 months of ketoprofen at approx. 250 mg/d, when it was stopped; 3 weeks later, SGOT was 100 and 49 in two tests on the same day, and SGOT was 115. Liver biopsy revealed "central lobular necrosis with endothelial injury in the hepatic vein tributaries", which the hepatologist from Mount Sinai School of Medicine, N.Y., Dr. F. Schaffner, considered to be "an acute rather than chronic toxic injury which may have been due to aspirin". N.B.: the patient took concomitantly 6 tablets of aspirin daily (L.O.).

In the opinion of the consulting gastroenterologist, G.E. Burdick, M.D., Phoenix, AZ, "the findings on liver biopsy were very mild and probably have no long-term implications."

(c) Clinical ADR

(c.a.) Neurologic/sensory:

48/94 (51.1%) of patients reported the following ADR:

tinnitus: 21 patients 44 times at 3.1% prevalence rate;

dizziness: 19 patients 37 times at 2.6% prevalence;

headache: 20 patients 36 times at 2.5%.

(c.b.) GI:

57/94 (60.6%) of patients reported the following ADR:

dyspepsia: 30 patients 68 times at 4.7% prevalence rate;

abdominal pain: 26 patients 46 times at 3.2% prevalence rate;

diarrhea: 18 patients 32 times at 2.2% prevalence;

nausea: 18 patients 29 times at 2.0%;

anorexia: 14 patients 17 times at 1.2% prev.;

flatulence: 5 patients 6 times at 0.4% prevalence;

nausea and vomiting: 5 patients 5 times at 0.4% prevalence rate.

(c.c.) Skin: 22 patients reported 33 times rash (unspecified).

(c.d.) General: 6 patients reported 6 times infection (unspecified).

In summary, 77/94 patients reported at least one ADR. Of the 84 patients participating in the open-label phase, 69 reported one or more ADR; 12/84 patients dropped out of the open-label phase because of ADR.

Furthermore, 29/94 patients, who participated in the first 3 months of treatment, did not report any ADR;

20/94 pts., who participated in the first 6 months of treatment, did not report any ADR;

73/94 patients were evaluated between month 3 and 6;
35/73 patients were ADR-free;

48/94 pts. were evaluated between month 6 and 12;
23/48 were ADR-free.

Conclusion: under the conditions of this trial (concomitant intake of up to 6 tablets of aspirin daily), it was impossible to assess the absolute or relative safety and efficacy of ketoprofen; this remark pertains also to central lobular necrosis with endothelial injury in the hepatic vein tributaries, described in par. (b.a.) above.

c. Study MDS-201A: "A Long-Term Safety Study of Ketoprofen in Rheumatoid Arthritis."

S. J. Alexander, M.D., P. J. Bilka, M.D., A. Calin, M.D. G. E. Ehrlich, M.D., W. H. Emori, M.D., A. L. Goldman, M.D., H. E. Montoya, M.D., J. L. Parsons, M.D.; and F. R. Schmid, M.D.

44 patients from Study MDS-201 (cf. par. IV.B.4. - double-masked, parallel) were added for evaluation of safety to this (MDS-201A) open-label study in which 141 patients, 95F, 46M, age 25-81, mean 51.6 years with the duration of the disease from 0.3 to 57, mean 10.4 years, received ketoprofen from 200 to 399 mg per day for 4-1175 days (=3 years and 3 months), mean exposure for the 185 patients being 500 days.

(1) Efficacy assessment

although a full assessment of efficacy was performed at each visit, the data were not statistically analyzed because this phase was unmasked and had no control group. Nonetheless, the open-label treatment was terminated in 42/141 patients for lack (or loss) of efficacy.

(2) Safety assessment

Since a total of 591 ADR were noted, the patients averaged one ADR every 156 days. Gastrointestinal ADR totalled 275 yielding an incidence of one GI ADR every 336 days. The total of neurologic/sensory ADR was 139, the incidence being one every 665 days.

During the first 3 months of treatment, 277 ADR were reported in 85 patients in 738 visits with 37.5% prevalence rats.

During months 3 thru 6 127 ADR were reported in 39 patients in 348 visits with prevalence rats of 36.5%.

After 6 months of treatment, 187 ADR were reported in 43 patients in 1022 visits, reducing the prevalence rate to 18.3% hence, the clinical ADR were less likely to occur later in the long-term trial.

The exact mean daily intake of ketoprofen could not be established in this study.

(a) Ophthalmologic examinations

31 patients had ophthalmologic examinations at baseline (within one month of starting ketoprofen treatment); 12/31 of these had follow-up examinations after 6 months of ketoprofen treatment.

An additional 20 patients (who began eye screening during the open-label trial) had no baseline examination but had follow-up examinations any time after one month of treatment.

Eye screening on long-term ketoprofen treatment (more than 18 months, maximum of 38 months) was done in 34 patients.

The following abnormalities occurring after at least one month of ketoprofen treatment were observed in 6 patients:

Dr. Calin, pt. # : small corneal scar O.S. at 16 months of treatment - not drug related;

Dr. Emori, pt. # : increase of pressure O.U. - upper limits of normal;

Dr. Goldman, pt. # : 21 mm Hg O.U. - considered not drug-related;

Dr. Montoya, pt. # : "arcus senilis and nuclear and cortical cataracts" noted 28 months after normal baseline, "probably not noticed in the previous examination."

Comment: the drug-induced, e.g., corticosteroids, cataracts are posterior subcapsular (L.O.).

Dr. Parsons, pt. # : reddish-brown pigment on the corneal epithelium of both eyes, most probably due to chrysotherapy.

Dr. Parsons, pt. # : "a fine carpet of pigmented cells on the inner lining of the cornea in both eyes" after 13 months of ketoprofen administration, disappearing one year later - apparently due to chrysotherapy.

(b) Clinical ADR

GI: 67/185 pts. with 275 occurrences.
Neurologic/sensory: 63/185 pts. with 139 occurrences.
General: 31/185 pts. with 81 occurrences.
Skin: 20/185 pts. with 49 occurrences.
Respiratory: 10/185 pts. with 17 occurrences.
Cardiovascular: 10/185 pts. with 13 occurrences.
Musculoskeletal: 9/185 pts. with 12 occurrences.
Genitourinary: 5/185 pts. with 5 occurrences.

(c) Dropouts due to ADR: 15/141 patients treated in the open-label phase:

3/15 dyspepsia
2/15 peptic ulcer
2/15 rash (1/2 due to gold Rx according to the inv.)
one of each: headache, gastritis, N & V, epistaxis, abd. pain, headache with rash, atrial fibrillation, and tinnitus.

(d) Prevalence rates:

months 0-3: 186 patients in 738 visits with 277 ADRs with 37.5% prevalence.

months 4-6: 140 patients in 348 visits with 127 ADRs with 36.5% prevalence.

Over 6 months: 120 patients in 1022 visits with 187 ADRs with 18.3% prevalence.

(e) Dose-dependent ADR:

somewhat paradoxically, more ADR occurred on the "low" dose level of ketoprofen (less than 250 mg/day, 330/817) than in the "high" dose level (more than 250 mg day, 256/1279).

N.B.: it is entirely possible that the patients on the higher dose of ketoprofen experienced more relief and, hence, reported less ADR.

Conclusion:

This long-term trial confirmed a satisfactory safety of ketoprofen in chronic treatment of rheumatoid arthritis. Ketoprofen exposure in the one-year, double-masked phase was followed by the open-label phase of up to 39 months with an average exposure of 500 days per patient for the population of 185 treated individuals; with this exposure, two patients developed peptic ulcers and the drug tolerance was seen to improve with duration of treatment.

- d. Study MDS-210A: "A Long-Term Multicenter Study of the Safety of Ketoprofen in Rheumatoid Arthritis." J. R. Caldwell, M.D. B. F. Germain, M.D., S. H. Lourie, M.D. G. E. McLaughlin, M.D., J. E. Poiley, M.D., P. D. Vreede, M.D., and C. H. Wilson, M.D.

This study describes the open-label trial (MDS-210A) which followed a double-masked parallel study comparing ketoprofen with indomethacin (MDS-210, reviewed by me in par. IV.B.6. above). The safety data collected during both phases are presented for the sake of continuity but the long term efficacy has not been analyzed because of the open-label nature of the second phase.

The results are based on all 125 patients who received ketoprofen under either of the two protocols; eleven of the patients receiving ketoprofen in the double-masked phase did not participate in the open-label phase.

(1) Duration of study:

The double-masked phase lasted 12 weeks. The open-label phase lasted 14-924 mean 451 days. The two phases combined lasted 17 - 1,008, mean 476 days.

(2) Dropouts due to ADR (8/125)

5/8 GI distress (1/5 was on ketoprofen for 418 days...; 4/5 remaining took ketoprofen for 1 to 6 months); 1/8 dizziness; 1/8 fainting spells; 1/8 tinnitus.

(3) Ophthalmological examinations

Of the 125 patients who were evaluated for safety, 116 had at least one examination, 110 had baseline examinations, and 102/110 of these had followup examinations.

5/53 with normal baseline had abnormal followup examination:

- (3.1.) metamorphopsia (distorted shape of objects - L.O.) - present after 3-month of ketoprofen, but not at the end of the 15-week ketoprofen administration.
- (3.2.) stromal hazing after 14-month ketoprofen administration - possibly ketoprofen - related.
- (3.3.) senile cataracts - not drug-related.

- (3.4.) "early senile cataracts" in a 43 year old female after 15 months on ketoprofen.

N.B.: since "senile cataracts" differ considerably from the posterior subcapsular cataracts observed, e.g., with corticosteroids administration, these cataracts were apparently not drug-related.

- (3.5.) color vision abnormality after 5 1/2-month ketoprofen administration - no followup confirmation of this finding.

Conclusion: 1/5 of the above described eye abnormalities can be classified (Karch-Lasagna classification - L.O.) as "possibly" ketoprofen - related.

(4) Clinical ADR related to ketoprofen

GI: 54 patients reported 152 ADR.*
Neurological: 30 pts. reported 75 ADR.
Cardiovascular: 3 pts. reported 5 ADR.
Genitourinary: 3 pts. reported 3 ADR.
Respiratory: none.
Skin: 8 pts. reported 13 ADR.
Musculoskeletal: none.
Other: 12 pts. reported 17 ADR.

*5 patients developed peptic ulcer and 4/5 of them subsequently dropped out; the mean duration of ketoprofen was 8 months (from 2 to 15) and the mean daily dose 253.0 mg.

(5) Laboratory tests abnormalities

Significant elevations of BUN occurred in 3 patients
(two of them with elevated BUN at baseline):

- (a) 65F with CHF, poorly controlled diabetes and intermittent hyperuricemia, receiving chronic diuretic treatment started ketoprofen with BUN of 29 mg% which gradually increased over the first year to 52 mg/dy; the values were then fluctuating below that level with the last measurement at month 25 being 45 mg%. She was discharged from the study after 770 days of ketoprofen treatment with a mode of 300 mg/day, supplemented by acetaminophen at average doses ranging mostly between 1,000 and 2,000 mg/day.

N.B.: note the perennial controversy about phenacetin's (and acetaminophen's) role in contributing to interstitial nephropathy (L.O.).

- (b) 68F on chrysotherapy and acetaminophen, started the trial with a normal BUN of 23 mg/dl which increased gradually to 43 mg/dl at month 19; all BUN values between months 14 and 31 were higher than normal the last value being 41 mg/dl. Massive number of RBC and WBC were seen in urine at Month 7, and to a lesser degree later, together with urinary casts and bacteria. This patient took ketoprofen 200 mg/day during her 930-day trial, in addition to acetaminophen about 2,500 mg/day, except during the last 9 months of the treatment.

N.B.: another case of interstitial nephropathy due to concomitant use of acetaminophen? (L.O.).

- (c) 74F on Dyazide for hypertension, started the double-masked phase with BUN of 27 mg/dl. During the 25-month ketoprofen treatment, BUN was consistently above that level and the maximum of 56 mg/dl was recorded at her last visit. No proteinuria was detected but the sediment repeatedly contained WBC and bacteria. She was progressively hyperuricemic. After 2 years of treatment, she experienced "subacute myocardial infarction", and was treated by Lanoxin, Lasix, and potassium; her ketoprofen treatment was terminated 2 months later at the conclusion of the trial as requested by the sponsor. She took acetaminophen sporadically only, while the ketoprofen dose was 300 mg/day.

(5.1.) Conclusion by the sponsor:

"The above three cases illustrate that even in patients with a history of cardiac disease and concurrent therapy the BUN increases were not associated with serious impairment of renal function. The three patients with the most marked and consistent BUN changes completed more than two years of ketoprofen treatment."

Remarks:

The first two case also suggest to me that there is a possibility of interstitial nephropathy in patients who take ketoprofen and acetaminophen concomitantly.

Hemoglobin

mean change from baseline at month 15 was -0.46 g/dl at $p=0.008$.

Hematocrit

mean change from baseline at month 15 was -1.13 mm/h at $p=0.025$.

BUN (cf. also par. 5.a. thru c. above):

mean change from baseline at month 27 was +2.19 mg/dl ($N=31$) at $p=0.007$.

Total serum protein

mean change from baseline at month 24 was -0.19 g/dl ($N=47$) at $p=0.008$.

Serum albumin

mean change from baseline at month 12 was +0.1 g/dl ($N=69$) at $p=0.026$.

SUA

mean changes from baseline were:

month 2: +0.33 mg/dl at $p=0.04$ ($N=55$)
month 18: +0.28 mg/dl at $p=0.04$ ($N=53$)
month 24: +0.36 mg/dl at $p=0.04$ ($N=44$)
month 27: +0.61 mg/dl at $p=0.008$ ($N=28$).

Conclusion

With the exception of two patients suggesting a possibility of drug-induced interstitial nephropathy with concomitant use of acetaminophen [par. (5) (a) (b) above], there were no clinically significant laboratory tests abnormalities.

- e. Study MDS-243: "An Open-Label, Multicenter Study of Evaluate the Safety and Efficacy of Ketoprofen in the Long-Term Treatment of Rheumatoid Arthritis."

Investigators: M.L. Brandon, M.D., J. R. Caldwell, M.D., A. L. Chodock, M.D., B. K. Guerin, M.D., W. M. O'Brien, M.D., G. E. McLaughlin, M.D., G. R. Parrino, M.D., L. M. Seebach, M.D., P. D. Vreede, M.D., and R. T. Reid, M.D.

Remark: this study was primarily designed as an open-label trial; it is not a continuation of an previously double-masked study.

252 adult patients with active, definite or classical R.A., 59F, 193M, age 24-81, mean 53.7 years, with the duration of the disease from 1-42, mean 10.0 years, 42 in stage 1, 131 in stage 2, 56 in stage 3, 6 in stage 4, and 17 in unrecorded stage, 43/252 on concurrent chrysotherapy, 7/252 on concurrent antimalarials, 62/252 on concurrent corticosteroids, 152/252 without concurrent therapy, received ketoprofen as follows:

250 pts. for 0-3 months mean 233 mg/day (99% remaining)
216 pts. for 3-6 months mean 262 mg/day (86%)
191 pts. for 6-9 months mean 266 mg/day (76%)
168 pts. for 9-12 months mean 269 mg/day (67%)
143 pts. for 12-15 months mean 268 mg/day (57%)
117 pts. for 15-18 months mean 272 mg/day (46%)
100 pts. for 18-21 months mean 273 mg/day (40%)
55 pts. for 21-24 months mean 275 mg/day (22%)
10 pts. for 24-27 months mean 283 mg/day (4%).

(1) Efficacy assessment

Although a full assessment was performed at each visit (baseline, weeks 4, 8, 12, 24, 36, and 48), the data were not statistically analyzed because this trial was unmarked and had no control group; however, dropouts for lack of efficacy were 48/252 (=19%).

(2) Safety assessment

safety variates were checked at baseline, at weeks 4, 8, 12, 24, 36, and 48.

(a) Dropouts due to clinical ADR (21/252)

15/21 dropouts were due gastrointestinal ADR, incl. 5/15 peptic ulcers and 5/15 epigastric pain (plus 1/15 abdominal pain;
3/21 dropouts were related to neurological/sensory ADR (paresthesias, vision abnormality, dizziness), and 2/21 to genitourinary system (urinary frequency, gross hematuria); 1/21 had fecal occult blood.

(b) Incidence of ADR

month 0-3: 81/252 patients reported 169 ADR during 966 visits with a prevalence rate of 17.5%;

month 3-6: 37/215 patients reported 52 ADR during 428 visits with a prevalence rate of 12.1%;

over 6 months: 47/191 patients reported 140 ADR during 1534 visits with a prevalence rate of 9.1%.

Conclusion: the incidence of clinical ADR decreased with successive treatment periods.

(c) Organ system distribution of ADR

gastrointestinal: 89/252 pts. = 35.3%
neurological/sensory: 42/252 pts. = 16.7%
general: 18/252 pts. = ~~7.1%~~ 7.1%
skin: 12/252 pts. = 4.8%
genitourinary: 10/252 pts. = 4.0%
respiratory: 10/252 pts. = 4.0%
musculoskeletal: 6/252 pts. = ~~2.4%~~ 2.4%
cardiovascular: 4/252 pts. = ~~1.6%~~ 1.6%
metabolic/endocrine: 1/252 pts. = 0.4%.

N.B.: 89 pts. with GI ADR reported 216 occurrences, while 42 patients with neurologic sensory ADR reported 79 occurrences.

(d) Laboratory abnormalities

The parametric analysis of laboratory variates showed statistically significant ($p = 0.05$) changes of the mean values at follow-up visits - when compared to baseline - for the following:

hemoglobin: -0.15 to -0.41 g/dl for 10 visits;
hematocrit: -0.22 to -1.11% during 9 visits;
BUN: +1.21 to +1.81 mg/dl during 10 visits;
SUA: +0.16 to +0.65 mg/dl during 10 visits;
total serum protein: -0.14 to 0.22 g/dl during 10 visits;
serum albumin: -0.05 to -0.12 g/l during 8 visits;
total serum bilirubin: -0.04 to -0.11 mg/dl during 5 visits.

Evaluation: *probably had any*

while statistically significant, none of the above mentioned mean changes ~~was~~ clinical significance.

When one, however, defines clinically relevant abnormalities as concurrent decrease from baseline of more than 1 g/dl for hemoglobin and more than 5% for hematocrit such a decrease occurred in 32/248 (12.9%) patients.

Similarly, when one defines clinically relevant abnormality as increase from baseline over 25 mg/dl for BUN, such an increase was observed in 29/248 (11.7%) patients.

Finally, clinically significant increase in SAP (not defined - L.O.) was observed in 1/248 patient, and an elevation of SGOT rate (defined as SGOT divided by the upper limit of the normal range with ratio 1.0) was observed in two patients, who, however, had no concomitant total bilirubin elevation.

Traces or slightly positive occult blood in stool at the end of the trial period were found in 13/248 (5.2%) patients.

(e) Special safety tests

(e.1.) Ophthalmologic examinations

Ophthalmologic screening at baseline was performed in 190/252 patients; 150/190 of these had at least one follow-up examination. Another 22 patients had at least one eye examination during the trial although they did not have one at baseline.

Eye examinations were performed on long-term treatment (more than 18 months, maximum of 29 months) in 65 patients.

Result: one pt. had a decrease of visual activity associated with macular pigmentary findings in O.S. which were interpreted as possible early macular degeneration, possibly drug-induced; however, this was not confirmed as the patient's acuity returned to normal on the next examination and the macular change was felt to be due to aging (Dr. Vreede, pt.).

None of the remaining patients showed any drug-induced changes - the eyes.

(e.2.) Audiograms were performed at baseline in 182/252 patients and followed by at least one examination in 133/182 patients; another 24 patients had audiograms without one at baseline. No ear toxicity was found.

(e.3.) EKG were performed at baseline in 190/252 patients with subsequent follow-up in 153/190; another 23 patients had EKG without a tracing at baseline.

EKGs were performed after 18 months of ketoprofen administration in 65 patients.

No cardiotoxicity was found.

(f) Vital signs

ketoprofen had no statistical effect on blood pressure and pulse rates body weight showed a statistically - but no clinically - significant mean increase of about one-half pound in the first two months.

(2.1.) Conclusions as to safety

- (a) The prevalence of peptic ulcers in this long-term study was 2%.
- (b) The prevalence of clinical ADR decreased with successive treatment periods (e.g., by about one-half after 6 months of ketoprofen administration).
- (c) The most common clinical ADR pertained to the gastrointestinal tract (35% of patients), followed by neurological/sensory ADR (17%).
- (d) The attribution rate compares favorably with some other NSAIDs:

13.6% attrition after 6 months;
33.9% ----- 1 year;
53.6% ----- 1 1/2 years;
78.0% ----- 2 years of Rx.

- f. Study MDS-122: "A Double-Blind Crossover Study to Compare the Efficacy and Safety of Ketoprofen with Placebo in Rheumatoid Arthritis." Wm. M. O'Brien, M.D. administered either ketoprofen, 2.5 mg per kg body weight, for one week, or placebo for one week, to 12 adult patients with active, definite or classical R.A., 9F, 3M, age 26-64, mean 52 years, with the onset of R.A. between 23 and 63, mean 43.6 years, and duration of the disease from 1.22, mean 8.3 years. 2/12 were in stage I, 5/12 in stage II, and 5/12 in stage III. After one-week the groups were crossed over in a double masked and randomized design.

(1) Efficacy assessment:

due to the small number of patients as well as numerous protocol violations, no statistical inference was performed.

(2) Safety assessments:

7/12 patients continued ketoprofen treatment on an open-label basis for up to 29 weeks. Maintenance gold and corticosteroids therapies were continued in 3 and 4 patients, resp. 5/12 patients violated the protocol by taking aspirin concomitantly.

(a) Clinical ADR:

all 12 patients reported an ADR; of the 36 incidences which occurred, 20/36 involved the GI tract, followed by 6/36 neurologic side effects.

5 ADR were rated as severe: 3/5 on ketoprofen (N & V, headache, diarrhea) and 2/5 on placebo (diarrhea, stridor).

(b) Laboratory tests:

no clinically significant changes.

- g. Study MDS-158: "A Double-Blind Crossover Study to Compare the Efficacy and Safety of Ketoprofen with Indomethacin in Rheumatoid Arthritis." A. L. Goldman, M.D. and R. W. Payne, M.D. administered for 4 weeks either ketoprofen, 50 mg q.i.d., or indomethacin, 25 mg q.i.d., in a randomized, double-masked design to 30 adult patient with active, definite or classical R.A., 26F, 4M, age 30-67 mean 52.4 years, with the onset of R.A. between 16-61, mean 41 years and duration of the disease from 1 to 37, mean 11.5 years; 9/30 were in stage I, 10/30 in stage II, and 11/30 in stage 3. After 4 weeks of treatment, the patients were crossed over to the other drug without a washout period.

(1) Efficacy assessment:

due to the absence of a washout period between the treatments, no analysis was performed on any efficacy variate.

(2) Safety assessment

(a) Dropouts due to ADR:

1 on ketoprofen ("neurologic side effects") vs. 5 on indomethacin (mostly GI).

(b) Clinical ADR:

neurologic: 10 pts. with 16 occurrences on ketoprofen vs. 13 pts. with 22 occurrences on indomethacin;
GI: 9 pts. with 18 occurrences on ketoprofen vs. 9 pts. with 21 occurrences on indomethacin;
Skin: 2 pts. with 4 occurrences on ketoprofen vs. 1 pt. with 1 occurrence on indomethacin;

(c) Laboratory tests:

no clinically significant changes.

h. Study MDS-268: "A Double-Blind Parallel Study to Compare the Efficacy and Safety of Ketoprofen, with Ibuprofen in Rheumatoid Arthritis."

P. D. Vreede, M.D. administered in a randomized, double-masked fashion and parallel for 24 weeks either ketoprofen, 50 mg q.i.d. or ibuprofen, 400 mg q.i.d. to 10 adult patients with active, definite or classical R.A., 6F, 4M age 36-73, mean 52.8 years, with onset of R.A. between 27 to 69, mean 44.9 years, and duration of the disease from 1-29, mean 7.9 years, 7/10 in stage I, 1/10 in stage II, and 2/10 in stage III. The dosage could be adjusted to 300 or 100 mg ketoprofen per day, or 2400 or 1200 mg ibuprofen per day.

The actual daily mean intake of ketoprofen ranged from 243 mg at week 2 thru 356 mg, at week 8 to 296 mg with a mean for the study of 280 mg/day; the mean daily intake of ibuprofen was 2078 mg.

(1) Efficacy assessment:

due to the small number of patients (N=10) and the fact that all patients had therapeutic levels (> 10 mg/dl) of salicylate (!), no statistical inference was performed.

(2) Safety assessment:

N.B.: In evaluation of safety, one has to take into account that all patients had also a therapeutic serum levels of salicylates.

(a) Vital signs and body weight

No clinically significant changes occurred in vital signs.

Slight increases in body weight were observed in both treatment groups and persisted throughout the trial, apparently due to sodium (water) retention.

(b) Laboratory tests

Mean baseline serum creatinine of 1.1 mg/dl increased to a mean 1.3 mg/d at the last laboratory examination in the ketoprofen-treated patients.

In 2 ketoprofen - and one ibuprofen-treated patients hemoglobin fell by 1-2 g/dl.

(c) Clinical ADR:

seven patients reported a total of 20 ADR ten for each drug:

GI: 7 ADR in 4 patients on ketoprofen vs. 5 ADR in 3 patients on ibuprofen;

neurologic: 2 ADR in 2 patients for each drug;

respiratory: 0 for ketoprofen vs. 2 ADR in 2 pts. for ibuprofen;

skin: 0 for ketoprofen vs. 1 ADR in 1 pt. for ibuprofen;

urinary: 1 ADR in 1 pt. vs. 0 for ibuprofen.

None of these ADR was severe except for dyspepsia in one ibuprofen pt. (dropout).

Conclusion:

one can arrive to the conclusion (not stated by the sponsor) that the concomitant use of ketoprofen and salicylates in the treatment of R.A. did not cause any additional clinical ADR.

- i. Study MDS-135: "A Double-Blind Crossover Study to Compare the Efficacy and Safety of Ketoprofen with ASA in Osteoarthritis."

Wm. M. O'Brien, M.D. was terminated prematurely due to the limited availability of patients (N=5) as well as the faulty crossover design (no washout between treatments).

Safety assessment:

with the exception of a duodenal ulcer that became symptomatic during the aspirin phase and was diagnosed on the second day of ketoprofen treatment, no clinically important ADR, including laboratory tests, were observed,

The dosage was 3 mg/kg body weight per day for ketoprofen, and 60 mg/kg body weight daily for aspirin, each for 2 weeks.

- j. Study MDS-169: "A Double-Blind Crossover Study to Compare the Efficacy and Safety of Ketoprofen with ASA and Placebo in Osteoarthritis."

David Kaplan, M.D., assigned randomly each of 24 patients with O.A., 22F, 2M, age 48-81, mean 65.5 years, with onset of the disease between 25 and 74, mean 54.8 years, and duration of DJD from 1-35, mean 10.6 years, to ketoprofen, 3 mg/kg/d body weight, aspirin, 60 mg/kg body weight per day or placebo for 4 weeks on each drug with no washout between treatments.

(1) Efficacy evaluation:

due to the absence of a washout period between treatments, protocol violations, as well as the small number of patients who completed all three phases of the study, no efficacy analysis was performed.

(2) Safety evaluation:

(a) Laboratory tests:

scattered, isolated clinically insignificant instances of abnormally high or low hematological values occurred.

The only frequent finding in the U.A. was bacteria with or without WBC in the urine.

Few patients had elevated blood glucose levels and BUN, none of these being clinically significant.

(b) Clinical ADR (# of pts./occurrences):

Neurologic: 4/4 ketoprofen vs. 7/12 aspirin vs. 4/7 placebo;

GI: 8/21 ketoprofen vs. 6/11 aspirin vs. 4/6 placebo;

Resp: 0 vs. 0 vs. 1/1 placebo;

Skin: 1/1 ketoprofen vs. 2/3 aspirin vs. 1/1 placebo;

General: 1/1 ketoprofen vs. 1/1 aspirin vs. 2/2 placebo;

total: 8/27 ketoprofen vs. 13/27 aspirin vs. 8/17 placebo; totally 15 pts. had 71 ADRs.

Severe ADR were reported as follows: of the 9 ADR, 3/9 occurred in ketoprofen pts: abdominal pain, dyspepsia, and headache, however, as many as 5 ketoprofen patients dropped from the study due to either GI or neurologic ADR.

k. Study MSD-275B: "A Long-Term Multicenter Study of the Safety of Ketoprofen in Osteoarthritis."

M. Albert, M.D., M. Brandon, M.D., and P. D. Vreede, M.D.

This report describes the open-label trial (MDS-275B) which followed a single-blind, dose-ranging study (MDS-275A); in the latter study, lasting for 4 weeks, patients received placebo for one week and ketoprofen for 3 weeks; the last day of the second phase (MSD-275B) which lasted from 14 to 439, mean 299 days; the two phases combined lasted from 21 to 462, mean 306 days.

39F and 18M, age 40-84, mean 65.5 years with the duration of osteoarthritis from 4 months to 33 years, mean 9.4 years, received the following mean daily dosages of ketoprofen: 1 month: 260 mg; 3-4 months: 254 mg; 6-7 months: 248 mg; 8-9 months: 293 mg; mean throughout the trial: 248.5 mg/day.

(1) Efficacy assessment:

not performed since the study was not masked and there were no controls.

(2) Safety assessment:

(a) Dropouts due to ADR (5/57):

3/5 flatulence with 1/3 leg edema: 1/5 epigastric distress; 1/5 edema in both legs.

(b) Clinical ADR (related to ketoprofen):

GI: 20 patients with 69 occurrences;
skin: 3 pts. with 5 occurrences;
neurologic/sensory: 3 pts. with 4 occurrences;
cardiovascular: 1 occurrence;
musculoskeletal: 1 occurrence;
edema: 5 pts. with 10 occurrences;
weight loss: 1 occurrence.

(c) Laboratory tests

Hemoglobin: statistically significant mean decrease of HB of -0.34 g/dl at month 1, -0.42 g/dl at month 12, and N.S. drop at month 15; these mean decreases had no clinical significance.

Serum creatinine: mean decreases of -0.12 mg/dl at month 3, -0.22 at month 6, -0.21 at month 9, and -0.27 at month 12; N.S. changes at week 1, 2 months 1, 2, and 15; these mean decreases of serum creatinine had no clinical significance.

Total serum protein: mean decreases of -0.21 g/dl at month 1, and mean increase of +0.29 g/d at month 6; N.S. at all other evaluation points. These fluctuations of TSP means had no clinical significance.

Serum albumin: mean decreases of -0.08 g/dl at week 2, -0.14 at month 3, -0.26 at month 6, -0.24 at month 9; N.S. at month 1, 2, 12, and 15. These fluctuations had no clinical significance.

BUN: mean increases of +1.53 mg/dl at week 1, +2.59 at week 2, +2.68 at month 1, +1.68 at month 6, +2.75 at month 12; N.S. at months 2 and 3, months 9 and 15.

N.B.: These BUN increases were not accompanied by concomitant serum creatinine elevation - in fact, serum creatinine showed mild decreases. The mean BUN increases are not clinically significant. Individually, only 3 patients had mild BUN elevations: 33, 30 and 35 mg/dl resp. (N=8-25 mg/dl); the first patient, 78F, developed pyuria and hematuria at the end of the treatment, while the second patient, M76, had proteinuria (only) in the last visits.

Conclusion (as to renal function):

since both of the patients had normal BUN at baseline, the above described BUN elevation with accompanying urinary findings are classified (Karch-Lasagna classification) as "probably" due to ketoprofen.

Occult blood in stool:

a positive final Hemoccult test was attributed in one patient to contamination, in another to hemorrhoids.

(c.1.) Conclusion as to laboratory tests

We agree with the sponsor's conclusion that "In spite of many statistical significances based on paired t-test, the clinical significance of observed changes is negligible. In this long-term safety trial, ketoprofen was shown to be a drug not presenting a serious (emphasis mine - L.O.) risk of toxicity to osteoarthritic patients, most of them elderly and suffering from a variety of chronic ailments, for which they received many concurrent drugs including diuretics.

N.B.: 39 patients (65%) were taking one or more concurrent medications: 23 of these took cardiovascular drugs, 18/23 of which taking a diuretic either antihypertensive agent; 7 patients (12%) took a neurologic drug, and 6 a gastrointestinal agent.

1. Study MDS-288B: "A Long-Term Multicenter Study of the Safety of Ketoprofen in Osteoarthritis."

Investigators: R. D. Brobyn, M.D., J. S. Johnson, M.D., J. I. McMillen, M.D., A. Miyara, M.D., and J. E. Poiley, M.D.

The study comprises two phases: the first, double-masked and parallel phase lasted 4 weeks in which the patients took either 200 mg per day ketoprofen, or 30 mg/day ketoprofen, or placebo; the second phase, during which the patients took in an open design either 100 mg/d, or 200 mg/d, or 300 mg/day of ketoprofen, lasted one year. Of the 95 patients discussed in this report, 90 were enrolled in

the open-label phase; 48/90 completed one year of open-label treatment and 13/48 completed from 13 to 15 months of treatment. There were total of 49F and 41M, age 40-87, mean 64.0 years, with the duration of the disease from 3 months to 35 years, mean 8.7 years. The six additional patients who took ketoprofen during the double-masked phase only, were all females age 57-78, mean 68.0 years with a mean duration of the disease of 7.0 years.

(1) Concurrent illness and concurrent therapy

73 patients (76%) were taking one or more concurrent medications: 53 pts. took cardiovascular drugs with 41/53 on diuretics, either alone or combined with an antihypertensive, 24/53 on gastrointestinal agents.

(2) Premature termination

48/90 completed approximately one year of treatment. The reasons for discontinuing treatment for the other 42/90 patients were: 18/42 lack of efficacy; 4/42 concurrent illness; 8/42 ADR: 2/8 nausea, 2/8 dyspepsia; one of each: constipation, hematemesis, peripheral edema, epigastric pain.

(3) Clinical ADR

GI: 31/96 pts. reported 79 occurrences;
neurologic/sensory: 12/96 pts. reported 20 occurrences;
skin: 4/96 pts. reported 4 occurrences;
respiratory: 1/96 pt. with 1 occurrence;
musculoskeletal: 1/96 pt. with one occurrence;
nonspecific pain: 1/96 pt. with one occurrence;
peripheral edema: 1/96 pt. with one occurrence;

(4) Laboratory tests

Hemoglobin: mean decreases of -0.33 g/dl at month 1
-0.21 at month 2, -0.29 at month 3,
-0.51 at month 6, -0.82 at month 9,
-0.76 at month 12, and -0.55 at "last visit."

Hematocrit: mean decreases of -0.85% at month 1,
N.S. at month 2, -0.64 at month 3,
-0.77 at month 6, -1.75 at month 9,
-1.81 at month 12, and -1.11% at "last visit."

BUN: mean increases of +3.45 mg/dl at month 1, +1.98 at month 2, +2.51 at month 3, +4.75 at month 6, +3.22 at month 9, +2.62 at month 12, and +2.48 mg/dl at "last visit."

(a) Effect of ketoprofen on BUN and creatinine in patients with normal baseline values for both:

N.B.: normal values for BUN were 8-25 mg/dl and for serum creatinine 0.7-1.5 mg/dl.

pt. # 12 months on ketoprofen: max. BUN = 31 mg/dl, final BUN = 21 mg/dl (creatinine maximum and final = 1.1 mg/dl); pt. took diuretic concomitantly;

pt. # 12 months on ketoprofen (no diuretic): max. BUN = 29 mg/dl, final BUN = 26 mg/dl; maximum creatinine = 1.7 mg/dl, final creatinine = 1.7 mg/dl;

pt. # 11 months on ketoprofen plus diuretic: max. BUN = 41 mg/dl, final BUN = 39 mg/dl; max. creatinine = 2.0 mg%; final creatinine = 1.3 mg/dl;

pt. # 13 months on ketoprofen plus diuretic: max. BUN = 28 final BUN = 28 mg/dl; max. creatinine = 1.8, final creatinine = 1.4 mg/dl;

pt. # 11 months on ketoprofen (no diuretic): max. BUN = 46 mg/dl, final BUN = 46 mg/dl; max. creatinine and final creatinine = 1.1 mg/dl.

pt. # 6 months on ketoprofen plus diuretic: max. BUN and final BUN = 31 mg/dl; max. creatinine and final creatinine = 1.1 mg/dl;

pt. # 9 months on ketoprofen plus diuretic: max. BUN = 35, final BUN = 31 mg/dl; max. creatinine = 1.4 final creatinine = 1.3 mg/dl;

pt. # 6 months on ketoprofen plus diuretic: max. and final BUN = 29 mg%; max. and final creatinine = 1.6 mg%;

pt. # 11 months on ketoprofen (no diuretic): max. and final BUN = 29 mg/dl; no creatinine done;

pt. # 11 months on ketoprofen (no diuretic): max. BUN = 29, final BUN = 20 mg/dl; no creatinine done;

pt. # 21 months on ketoprofen (no diuretic): max. BUN = 35, final BUN = 30 mg/dl; no creatinine done;

pt. # 13 months on ketoprofen (no diuretic): max. BUN = 36, final BUN = 30 mg/dl; no creatinine done;

pt. # , 6 months on ketoprofen (no diuretic): max.
BUN = 37 mg/dl, final = 31 mg/dl; no
creatinine done;
pt. # 12 months on ketoprofen plus diuretic; max.
BUN = 29 final BUN = 27 mg/dl; max.
creatinine = 1.5 final creatinine = 1.4
mg/dl.
pts. # and # had also increased BP.

(a.1.) Evaluation

The BUN elevations were accompanied in 2/14 patients by slight maximum and final increases of serum creatinine, in 2/14 additional patients by slight maximum but not final increases of creatinine; there were no concomitant serum creatinine increases in the remaining 5/14 patients in whom both tests were performed.

(a.2.) Conclusion:

a one-year ketoprofen administration caused mild to moderate BUN elevations in 14/96 patients, in 2/14 of which the elevations became normal in spite of continuation of the treatment. In 2/14 patients, the BUN elevations were accompanied by persistent but mild increases of serum creatinine.

Occult blood in stool

8/96 pt. had trace or positive Hemoccult responses; 7/8 had no more than two trace or positive responses, all 7/7 of which were negative at the final examination. 1/8, 69M, had 4 trace or positive responses, 1/4 of which occurred at the final examination; the investigator attributed these responses to the patient's diet (? why - L.O.).

There were no dropouts due to laboratory tests abnormalities.

(5) Ophthalmological examinations

Three eye examinations, one baseline and two follow-up had been scheduled, and 77/96 patients completed the baseline and at least one follow-up examination. 4/77 patients had eye changes:

, F54: endothelial fold;
F72: pigmentary changes;
M79: "early cataracts" - no details given;
, M72: do.

Remarks: due to the age of the last two patients, the cataracts were probably of the senile type, not posterior-subcapsular (as seen in corticosteroid therapy - L.O.

(6) Conclusion:

except for 8/96 dropouts due to gastrointestinal ADR, we agree with the sponsor's conclusion that:

"Ketoprofen in mean daily oral doses ranging from 173.2 to 296.2 mg (means per visit), when taken by patients with symptomatic osteoarthritis of the hip or knee, was demonstrated to be safe in a two-phase clinical trial of a scheduled duration of 12 or 13 months."

m. Study MDS-289B: "A Long-Term Multicenter Study of the Safety of Ketoprofen in Osteoarthritis."

Investigators: H. M. Adelman, M.D., R. D. Brobyn, M.D., J. R. Caldwell, M.D., J. I. McMillen, M.D., and E. L. Tarpley, M.D.

The study comprises two phases: the first, double-masked and parallel phase lasted 12 weeks in which the patients took either 200 mg per day ketoprofen, or 2600 mg/day aspirin, both on a q.i.d. basis; the second phase, during which the patients took in an open design either 100 mg/d, or 200 mg/d, or 300 mg/day of ketoprofen lasted for a mean of 297 days; the mean duration of the two combined phases was 310 days.

A total of 74 patients are discussed in this report, of whom 69/74 were enrolled in the open-label phase. 47/69 (=68%) completed one year of open-label treatment, and 18/47 went on to complete from 13 to 16 months of therapy. There were 48F, 21M, age 35-83, mean 62.7 years, with the duration of O.A. from 1 to 45, mean 9.3 years. The five additional patients who took ketoprofen during the double-masked phase only, were 3F, 2M, age 56-73, mean 65.2 years, with the duration of O.A. from 1-22, mean 8.6 years.

(1) Concurrent illness and concurrent therapy

51/74 (=69%) patients were taking one or more concurrent medications: 30 pts. took cardiovascular drugs with 28/30 on a diuretic, either alone or combined with an antihypertensive, 15/30 on gastrointestinal agents.

(2) Premature termination

47/69 (=68%) pts. completed approximately one year. The reasons for discontinuing treatment for the other 22/69 patients were:

9/22 lack of efficacy;
1/22 concurrent illness;
3/22 ADR: constipation and edema; dyspepsia; pain in chest and abdomen (all moderate); the first patient completed 284 days, the second and third pt. completed 14 and 57 days of ketoprofen Rx, resp;
9/22 for other reasons, incl. noncompliance and surgery.

(3) Clinical ADR

GI: 17/74 patients (23%) reported 25 occurrences;
neurological: 2 patients reported 2 occurrences;
cardiovascular: 2 patients reported 3 occurrences;
genitourinary: one pt. reported 5 occurrences;
skin: 1 pt. with 1 occurrence;
other (edema): one pt. with 3 occurrences.

(4) Laboratory tests

Hemoglobin: mean decreases of -0.27 g/dl at month 2, -0.34 at month 3, -0.21 at month 6, -0.33 at month 9, -0.31 at month 12, -0.48 at month 15 and "last" 0.42 g/dl (NS at month 1).

Hematocrit: mean decreases of -0.95% at month 2, -1.22 at month 3, -1.11 at month 12, -1.72 at month 15, and "last" -1.55% (NS at month 1, 6, and 9).

Total serum protein:

mean decreases of -0.32 g/dl at month 1, -0.18 at month 2, -0.19 at month 3, -0.20 at month 9, -0.24 at month 12, -0.44 at month 15, and "last" -0.25 g/dl (NS at month 6).

Lymphocytes: mean decreases of $-22.21/\text{mm}^3$ at month 2, -25.77 at month 3, -37.22 at month 6, -39.85 at month 12, and "last" $-27.97/\text{mm}^3$ (NS at months 1, 9, and 15).

Isolated changes of means were found for total serum bilirubin (high at week 2 of $+0.10 \text{ mg/dl}$ decreased by 0.07 mg/dl at the "last" visit), BUN (increased by 1.65 and 1.73 mg/dl at months 3, and 6, resp.), SUA (decreased by 0.60 and 0.45 mg/dl at months 1 and 15, resp.) and serum albumin (decreased by 0.15 , 0.08 , and 0.10 g/dl at month 1, 3, and at the "last" visit.

(4.a.) Discussion of laboratory tests

BUN: of 21 patients with normal baselines who had increases at any time during therapy, 15 of those increases were transient and returned to normal by the final visit while 6 remained slightly elevated at the last visit; none of these elevations caused any clinical concern except in pt. # who took an overdose of 800 mg/day for about 5 day because she (66 y. old) misunderstood the dosing instructions; her BUN was 46 mg/dl before the overdose, and dropped to 31 mg/dl 23 days after the overdose; serum creatinine rose gradual by after the baseline, but was WNL until the final visit when it was 1.7 mg/dl (Normal 1.5 mg/dl); this pt. was on Lasix, Inderal, Apresoline, and Slo-K concurrently with ketoprofen.

No patients were withdrawn from the study because of laboratory test abnormality.

(5) Ophthalmological examinations

55 patients had baseline and at least one follow-up eye examination, while 18 had only the baseline and one no examination at all.

6/55 patients had changes during the treatment none of which was considered to be ketoprofen related:

2/6 developed senile nuclear lenticular changes; 1/6 had Hudson - Staht lines which occur only in elderly patients; 1/6 had borderline pressures at baseline, but increases to 20 mm Hg O.D. and 21 O.S. ; 2/6 developed "early cataracts" (no location given, but apparently they were not posterior subcapsular, since they were considered not be drug-related - L.O.).

(6) Conclusion:

as in previous studies, gastrointestinal were the most commonly occurring clinical ADR, necessitating premature termination in 3/69, alas, after... 284 days of ketoprofen administration in one patient.

There were statistically - but not clinically-significant changes in laboratory tests, none ~~of which~~ necessitating a premature termination.

n. Study MDS-X: "Long-Term Extension Multi-Clinic, Open Study of Ketoprofen in Patients who had been Exposed to Ketoprofen for at Least 12 months."

Investigators: G. B. Bluhm, M.D., A. L. Goldman, M.D., S. S. Hartman, M.D., J. Hyla, M.D., J. S. Johnson, M.D., E. H. Krick, M.D., J. I. McMillen, M.D., L. M. Seebach, M.D., and P. D. Vreede, M.D.

This report describes partial results of an ongoing multi-center, long - term open-label study of patients previously enrolled in one of the following studies: MDS-189, -201, -210, -243, -275, and MDS-288. There were 38F, 34M, age 24-78, mean 54.3 years, 55/72 with R.A., 17/72 with O.A., with duration of ketoprofen therapy from 1.0 to 2.9, mean 1.6 years; 37/55 R.A. pts. had no background therapy, while 18/55 took either gold (15/18), or antimalarial (1/18), prednisone (1/18), or gold and prednisone, concomitantly.

(a) Concurrent medication was taken by 71/72 patients, the mode being diuretics.

(b) Treatment termination

51/72 patients terminated the treatment before the data were analyzed; the reasons were:

15/72 (20.8%) lack of efficacy;
7/72 (9.7%) ADR: 2/7 peptic ulcer, one of each: stomatitis, pruritus, diarrhea, dyspepsia, nausea with somnolence.
29/72 (40.3%) other reasons, mostly lost to follow-up and transfer to another study;
3/29 dropped for the following reasons:

1/3 lichen planus after 33 months of Rx;
1/3 diverticulitis after 16 months of Rx;
1/3 anemia after 18 months of Rx.

(c) Medication consumption

53/72 pts. had a mean consumption of 300 mg ketoprofen/day; 1/72 had a mean of 400 mg/day; 4/72 had 250 mg/day, 9/72 200 mg/d.

(d) Safety assessment

69/72 were included in the safety assessment (3/72 had no follow-up).

(d.1.) Laboratory tests:

BUN: 2/69 increases: 1/2 pt. from 20 mg/dl at baseline to 31 mg/dl after 19 months of ketoprofen Rx (serum creatinine was 1.0 mg/dl at all times); 1/2 pt. from 25 mg/dl at baseline to 35 mg/dl after 7 1/2 months of Rx with concomitant elevation of serum creatinine of 1.6 mg/dl at baseline to 2.1 mg/dl after 7 1/2 months.

Hb and Hct

1/69 pt. who received ketoprofen for 27 months (when he was dropped from the study for...lack of efficacy) had baseline Hb of 13.4 g/dl which decreased gradually to 10.7 g/dl at the last visit; the Hct decreased correspondingly from 41 to 33%. No gastrointestinal bleeding was detected in this patient.

Occult blood in stool

17 positive or trace Hemoccult tests were found in 252 patient visits; these 17 positive findings were observed in 11 patients in 9 of which they were isolated occurrences. The remaining 2 patients had a chronic low-grade anemia which did not require treatment:

1/2, 69F, diabetic with diverticulitis, was diagnosed as anemic after 33 months of ketoprofen therapy and placed on iron therapy, positive Hemoccult tests were reported at months 6, 9, and 12.

1/2, 41M, with rectal fissures, received ketoprofen for 22 months when he was transferred to another study; his Hb ranged from 13.4 to 13.9 g/dl, his Hct from 38 to 42%; positive Hemoccult tests were reported at months 3, 6, and 15 (not done at month 18).

Comment: diverticulitis in the first case, and rectal fissures in the second could account for the occult blood in stool.

(d.2.) Clinical ADR

gastrointestinal: 13 patients with 23 occurrences
neurologic/sensory: 5 patients with 5 occurrences
skin: 2 patients with 3 occurrences
cardiovascular: 2 patients with 2 occurrences
endocrine: 1 patient with 3 occurrences
general: 1 occurrence.

The most common GI ADR was dyspepsia, reported 10 times by 6 patients as mild or moderate. As already mentioned above [par. (b.)], 7/72 patients dropped out due to clinical ADR.

Conclusion

with the exception of the 10% dropouts due to clinical ADR, we agree with the sponsor's conclusion that "...ketoprofen is a safe drug in the long-term treatment of patients with rheumatoid arthritis and osteoarthritis."

- o. Study MDS-142: "A Double-Blind Crossover Multicenter Study to Compare the Efficacy and Safety of Ketoprofen with Aspirin in Rheumatoid Arthritis."

Investigators: C. H. Alexander III, M.D., R. A. Blau, M.D., R. F. Jacox, M.D., S. B. Kaplan, M.D., Wm. M. O'Brien, M.D., F. R. Schmid, M.D., R. A. Turner, M.D., and R. F. Wilkens, M.D.

A publication resulting from this study by O'Brien, Wm., Sakofsky, HY, and Schmid, RF entitled "A Controlled Double-Blind Study of Ketoprofen Versus Aspirin in the Treatment of Rheumatoid Arthritis" appeared in Curr Ther Res 21:689-696, 1977.

Remark: Since there was no washout between the two active drug phases, meaningful statistical assessments could not be obtained from the data collected during the second drug phase; however, there was a washout prior to the first drug phase; therefore, only the safety data and global assessment from the first drug phase were statistically analyzed.

N.B.: The trial commenced in March 1974 and was completed in June 1975.

63 adult patients with active, definite or classical R.A., 44F, 19M, age 26-78, mean 51.8 years, with the duration of the disease from 1-40, mean 10.8 years received for 4 weeks either ketoprofen, 3 mg/kg body weight per day (32/63 pts.), or aspirin, 60 mg/kg/day, and were then crossed over to the other drug for another 4 weeks without an interdrug washout. The trial was preceded by an one-week placebo washout.

The ARA stage was I in 18/63, II in 34/63, III in 8/63, IV in 2/63, and not recorded in 1/63 patients. 9/63 were on concomitant stable chrysotherapy.

(1) Premature termination

48/63 pts. completed both phases; 9/63 completed only phase 1, 2/63 only phase 2, and 4/63 did not complete either phase.

There were 5/63 dropouts due to clinical ADR in the aspirin phases (nausea; tinnitus, dyspepsia) and no dropouts due to ADR in the ketoprofen phases.

1/63 in the ketoprofen phases and 4/63 in the aspirin phases dropped due to lack of efficacy.

(2) Medication consumption and compliance

The mean daily consumption of ketoprofen was 226.2 mg during phase 1 and 183.5 mg during phase 2, which represents a compliance of 98.4% and 93.4%, resp. Mean daily consumption of aspirin was 3539.8 mg during phase 1 (89.9% compliance) and 3510 mg during phase 2 (88.0% compliance).

(3) Concomitant medication

53/63 pts. took concomitant medication, mostly diazepam, propoxyphene and acetaminophen.

(4) Efficacy assessment

Interdrug comparisons at week 4 showed mean improvement in the ketoprofen group as judged by investigator's global assessment to be statistically superior to that of aspirin-treated patients at $p=0.024$.

(5) Safety assessments

(a) Laboratory tests

statistically significant changes occurred in 2 ketoprofen-phase means: -0.34 g/dl decrease from baseline in hemoglobin, and -0.19 g/dl decrease from baseline in total serum protein ($p=0.01$ and 0.02 , resp.), and in 9 aspirin-phase means (BUN, SUA, total bilirubin, etc.).

Hemoglobin

5/63 decreases over 2 g/dl in the ketoprofen phase vs. 1/63 decrease in the aspirin period.

BUN

increase - but still WNL - observed in 5 aspirin-phase patients.

SGOT

69F, who completed phase 2 (ketoprofen) had 165 mn/dl (ratio 4.1) at the end of trial; her SGOT fluctuated during the study and was slightly elevated at 3 determinations, one of which was accompanied by an increase in total serum bilirubin of 2.0 mg/dl (week 1); no follow-ups were available, however, at the final determination the total bilirubin was normal (0.2 mg/dl).

Occult blood in stool

one ketoprofen - phase pt. and 2 aspirin - phase pts. had positive Hemocult test, in addition to one pt. in the placebo - washout phase.

(b) Clinical ADR

(b.1.) Dropouts due to ADR:

0 ketoprofen vs. 5 aspirin - phase patients.

(b.2.) ADR according to organ system

GI: 32 ketoprofen vs. 33 aspirin pts.;
neurologic/sensory: 23 ketoprofen vs. 33 aspirin
pts.;
skin: 6 ketoprofen vs. 7 aspirin pts.;
general: 5 vs. 5;
cardiovascular: 2 vs. 1;
respiratory: 1 vs. 2;
genitourinary: 2 vs. 1;
musculoskeletal: 1 vs. 1.

Remark: none of these differences is
statistically significant, however,
tinnitus was found to be significantly
($p=0.003$) more frequent during the
aspirin phase.

(6) Conclusion:

while we agree with sponsor's conclusion that
"...ketoprofen was demonstrated to be a safe
anti-inflammatory agent in the treatment of rheumatoid
arthritis", this statement is of minor significance,
considering the brief duration of drug administration (4
weeks).

K. SUMMARY OF BASIS OF APPROVAL (continued):
SUPPORTIVE STUDIES - FOR SAFETY ONLY:

1. RHEUMATOID ARTHRITIS

The approval of ketoprofen for the indication of rheumatoid
arthritis is further supported by four open-label studies of 646
patients who took ketoprofen for up to over 3 years, mean
approximately 16 1/2 months and generally experienced similar
clinical adverse reactions as those described in the adequate
and well-controlled studies in par. IV.B. above; of particular
significance is that fact that no prohibitive ophthalmological
adverse reactions were found in 201 patients who took ketoprofen
for 18 to 38 months (cf. studies MDS-189A, -201A, -210A, and
-243 above).

[There are also five double-masked, 3/5 crossover, 2/5 parallel
studies of 162 patients who received ketoprofen in comparison to
placebo indomethacin, ibuprofen, or aspirin, for up to 29 weeks;
however, these studies were poorly designed, allowing either
concomitant intake of aspirin (4/5 studies), or not having a
washout between crossover (1/5 study) (cf. studies MSD-189,
-122, -158, -268, and -142 above)].

2. OSTEOARTHRITIS

The approval of ketoprofen for the indication of osteoarthritis is further supported by four open-label studies (MDS-275B, -288B, -289B, -X above) of 288 patients who took ketoprofen for up to 2.9 years, with a mean of 300 days in one study, and 1.6 years in another, and generally experienced similar clinical adverse reactions as those described in the adequate and well-controlled studies in par. IV.D. above; of particular interest is the fact that no prohibitive ophthalmological adverse reactions were found in 55 patients who took ketoprofen for up to 16 months.

[There are also two double-masked and crossover studies, one of 5 patients, terminated because of too small number of subjects, the other of 24 patients who took either ketoprofen or placebo for 4 weeks, and were then crossed over (MDS-135 and MDS-169); in the latter, the previously known, mostly gastrointestinal, ADR were encountered.]

L. LABELING

Packaging circular

1. DESCRIPTION:

structural and molecular formulae, and molecular weight correct.

2. CLINICAL PHARMACOLOGY

- a. The statements pertaining to clinical pharmacology are documented by me in par. I.J., III!. A. thru K., and IV.A.1. thru 14. above as well as 26 literature references.
- b. The indications for rheumatoid arthritis are documented in this MOR in par. IV.B. and C, those for osteoarthritis in par. IV.D. and E., for
in par. IV.F. and G., and for
in par. IV.J. above.
- c. I do not consider the study in
as an adequate and well-controlled trial and recommend disapproval of this indication (par. IV.H.).

The sponsor also quotes ten literature references in support of the four indications mentioned in the above second paragraph.

- d. ad ref. #36: "The side effects tended to be less frequent with Orudis than with indomethacin."

Comments: this statement should be deleted since the interdrug differences did not reach statistical significance.

- e. ad ref. #31: "In one study, the comparative drug indomethacin showed a small average increase in blood pressure; the difference between the two populations was statistically significant different at the end of treatment."

Comments: this statement should be deleted since this difference was statistically significant at week 4 only, and, furthermore, it had no clinical significance anyhow.

- f. In the same paragraph: "Furthermore, in the pooled population of two-indomethacin controlled trials, ketoprofen was found to cause significantly fewer neurological/sensory adverse reactions than indomethacin."

Comment: this statement should be deleted since no evidence for it is submitted.

- g. In view of par. c. above, the entire following paragraph should be deleted:

"Improvement in patients treated for acute gouty arthritis has been shown by prompt relief of pain at rest, and on active and passive motion, and a remission of symptoms as assessed by investigator and patient. Most patients experienced relief of pain within 4 hours after the first dose and all patients reported substantial pain relief within 12 hours of the first dose."

3. INDICATIONS and USAGE:

delete par. "5.
as

" twice and "as well

4. CONTRAINDICATIONS:

acceptable.

5. WARNINGS: acceptable.
6. PRECAUTIONS: acceptable.
7. ADVERSE REACTIONS

This section contains the irrational listing of clinical ADR under 3 (three) different headings, namely, "Incidence greater than 1%", "Incidence less than 1%" and "Causal Relationship Unknown", thus forcing the busy practitioner - for whom the labeling is envisaged to look at 3 (three) different places for a specific organ adverse reaction, e.g., dermatological or CNS ADR for this NDA.

The prevalence (it is no "incidence" - L.O.) should be listed under organ systems, e.g. dyspepsia 10% (or 1 in 10) under gastrointestinal ADR.

M. RECOMMENDATION

Approval of NDA 18-754 with the labeling changes as proposed by me in par. L. above.

F.T. received on 8-30-85.

Leszek Ochota

Leszek OCHOTA, M.D., Sc.D.

Orig NDA 18-754
HFN-150/Div File
HFN-150/Pease
Draft Completed: 08-19-82
Finally Typed by: P. Amoss/8/9/84
Finally corrected by DL 8/19/85
First 40 pages typed by DGarrison
Wang #3207P

N-18754

ANALYTICAL METHODS

100-1000

100-1000

100-1000

METHODS VALIDATION REQUEST AND REPORTING RECORD

NDA NO.

18754

SAMPLES BEING FORWARDED		CONTROL NO. OF OTHER IDENTIFICATION	
ITEM	QUANTITY		
Ketoprofen, Active Ingredient	2 bottles (15 grams)	Lot No. CA 7823000	
Ketoprofen Capsules, 25 mg.	2 bottles (225 capsules)	412A-T-145	
Ketoprofen Capsules, 50 mg.	2 bottles (225 capsules)	412A-T-143	
Ketoprofen Capsules, 75 mg.	2 bottles (225 capsules)	412A-T-144	
Ketoprofen Capsules, 100 mg.	2 bottles (225 caps)	412A-T-142	
Reference Standard -	2 bottles (250 mg)	Lot No. GES 252	
TLC Comparison Standard - RP 23,673	2 bottles (250 mg)	Lot No. HEN 776	
TLC Comparison Standard - RP 24,336	2 bottles (250 mg)	Lot No. FAB 991	
TLC Comparison Standard - RP 24,075	2 bottles (250 mg)	Lot No. CORBIN 20-1	
TLC Comparison Standard - RP 23,561	2 bottles (250 mg)	Lot No. PON 976	
TLC and System Suitability Reference	2 bottles (250 mg)	Lot No. ROL 2 915	
RP 33,601			
2. Photocopies of these items are attached:	Statement of Composition of Finished Dosage Form(s)	No. of Pages	NDA Page Number(s)
	Specifications/Methods for New Drug Substance(s)	7	3-6
	Specifications/Methods for Finished Dosage Form(s)	5	26-30
	Results of Determinations obtained by Applicant(s)	11	31-41
	Other: (Specify)	18	7-25
Description of active ingredient		2	1-2
3. REQUESTED DETERMINATIONS (Perform tests indicated below: (conduct ASSAY tests in DUPLICATE.)		4. SUMMARY OF RESULTS (Report individual and average ASSAY results)	
a. Drug Substance(s):		ASSAY	
1. Identification		25 mg capsules	
a. Infra-Red		1. 25.0 mg/cap, 100.0% of declared	
b. Ultra-Violet		2. 25.0 mg/cap, 100.0% of declared	
2. Thin layer chromatography		100 mg capsules	
a) RP-22,551		1. 99.1 mg/cap, 99.1% of declared	
b) RP-23,673		2. 100.0 mg/cap, 100.0% of declared	
c) RP-24,075		Avg. 99.5 mg/cap, 99.5% of declared	
d) RP-24,336		Identification	
3. Thin layer chromatography		25 & 100 mg capsules	
a) RP-33,601		HPLC retention times & IR-posit	
b. Dosage Form(s):		CONTENT UNIFORMITY	
4. Assay		25 mg capsules - passes	
a) Dosage Form(s)		1. 101.2%	
1. Identification		2. 103.2%	
a) Retention time in HPLC assay		3. 98.4%	
b) I.R.		4. 102.0%	
2. Dissolution		5. 98.4%	
a) 25 mg and 100 mg capsules		6. 98.4%	
3. Content Uniformity		7. 98.4%	
a) automated U.V. Spectrophotometry		8. 104.0%	
25 mg and 100 mg tablets		9. 100.0%	
4. Assay		10. 100.0%	
a) HPLC (on 25 mg and 100 mg caps)		100 mg capsules - passes	
		1. 100.5%	
		2. 93.2%	
		3. 101.1%	
		4. 96.5%	
		5. 101.7%	
		6. 95.3%	
		7. 98.7%	
		8. 98.7%	
		9. 98.7%	
		10. 97.5%	
SIGNATURE OF ANALYST		DATE	
Jean B. C. R. Hill 3494		11/15/92	
DISTRICT LABORATORY COPY ROUTING		DIVISION OF DRUG CHEMISTRY COPY ROUTING	
Division of Drug Chemistry (HFD 420)		Chemist (HFD-)	
Chemist (HFD-)		District Laboratory (HFD-)	
Field Sciences Branch (HFD-130)		Field Sciences Branch (HFD-130)	

HPLC System Suitability Tests: NDA 18-754, p. 34

Resolution: USP XX p. 945

$$R = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

t_1 & t_2 : retention time of the 2 components.
 W_1 & W_2 : widths of the bases of the peaks
obtained by extrapolating the straight
sides of the peaks to the baseline.

measurements obtained from standard injection
no. 6, run #19.

see assay for instrument conditions.