

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-676**

BOEQUIVALENCE REVIEW(S)

MAY 25 1995

Ketoprofen Tablet/Caplet, OTC
Actron[®], 12.5 mg
NDA 20-499
Reviewer: Ruth E. Stevens, Ph.D.

Miles Inc. (Bayer)
West Haven, CT 06516
tel. # 203-937-2693
Submission Date: 7/15/94

BACKGROUND:

The Sponsor, Miles Inc. (which has officially changed its name to Bayer), has submitted Actron[®] (ketoprofen, 12.5 tablets and caplets) to be marketed over-the-counter (OTC) for the following indications: temporary relief of headache, backache, muscular aches, toothache, minor pain of arthritis, menstrual cramps, minor aches and pains associated with the common cold, sore throat, and reduction of fever. Recommended dosing will be 12.5 mg to 25 mg every 4 to 6 hours, with a total daily dose of 75 mg. Ketoprofen tablets and caplets, 12.5 mg are manufactured using the same ingredients and manufacturing process: the only difference is the shape (the tablets are round and the caplets are capsule shaped).

Ketoprofen is currently marketed in the United States as Orudis[®] by Wyeth-Ayerst Laboratories. The product is available by prescription in 25, 50, and 75 mg capsules (NDA 18-754) and approved for rheumatoid arthritis, osteoarthritis, and mild to moderate pain. A 200 mg extended release product (Oruvail[®]) was recently approved for use (NDA 19-816).

SYNOPSIS:

There were a total of 5 studies submitted to the pharmacokinetic section of the NDA. In the initial formulation finding process, Miles, Inc. considered two manufacturing processes for the tablet. The two processes were The process was eventually selected for further development based on three criteria. The first two criteria were formulation and stability considerations and the last criteria was that the plasma concentration profile of the tablets matched closely the concentration versus time profile of Orudis[®]. Two studies were considered pivotal (clinical vs. 'to-be-marketed' formulation and dose proportionality) and the remaining three studies were considered supportive (2 dose proportionality studies). Assay validation was provided for all the studies on the compound. The assays were performed by

In addition, Study 0284 (supportive dose proportionality study) provided assay validation for the enantiomers of ketoprofen. The pivotal studies used the 'to-be-marketed' formulation.

RECOMMENDATION:

From a Biopharmaceutics standpoint, the Sponsor has submitted sufficient pharmacokinetic information for the approval of Ketoprofen 12.5 mg Tablet/Caplet (NDA 20-499) for over-the-counter marketing. A recommended dissolution method and specification for ketoprofen tablets would be:

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I. INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. Ketoprofen is currently available in the United States in higher immediate release strengths (25, 50, 75 mg). It is currently approved at a total daily dose of 150 to 300 mg for acute or long-term treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis. The Sponsor feels that a 12.5 mg dose of ketoprofen is an effective analgesic for mild to moderate pain and proposes to market this dose as an OTC product.

Ketoprofen itself has been the subject of numerous publications, both pharmacokinetic and clinical. Peter Lockwood, MSc., in his review of NDA 19-816 (Oruvail[®] 200 mg slow release tablets) and the Sponsor did a review of the published ketoprofen literature. In general, ketoprofen has been shown to be well absorbed orally with peak plasma concentrations occurring within 1 hour. Ketoprofen has a relatively small volume of distribution (0.1 L/Kg) and a short half-life of approximately 2 hours. It is 99% bound to plasma proteins. The metabolism of ketoprofen in humans follows two pathways:

Ketoprofen is excreted predominantly as the glucuronide

conjugate in the urine. In humans, 85% to 99% of ketoprofen and its metabolites are excreted in the urine rather than the feces.

II. BIOEQUIVALENCE

The clinical batch was bioequivalent to the production batch (AUC and Cmax were within the bioequivalence criteria of 80-125% for Ln transformed data).

Study S91-005 (page 24) was a three-way crossover study conducted in 30 healthy male subjects. The clinical batch was compared to the production batch. Both the clinical and production batch used the process. In addition, a single, marketed, 25 mg ketoprofen capsule (Orudis[®]) was tested to provide a general reference, but not used to evaluate bioequivalency. Table 1 provides the pharmacokinetic parameters and 90% confidence interval based on Ln transformed data. Comparing the 12.5 mg Miles clinical batch capsule and the 12.5 mg Miles production scale tablets, the 90% confidence interval based on Ln transformed data for AUC_{0-inf} and Cmax were well within the 80%-125% acceptance range (98%-104% and 97-122%, respectively). Many of the individual plasma profiles of ketoprofen often show more than one peak. Even though the multiple peaks result in a relatively high variance in Cmax, the 30 subject study resulted in a power of 81% to determine a 20% difference had it existed.

Table 1: Mean ± SD Pharmacokinetic Parameters for Orudis[®] 25 mg Capsule, Miles Clinical Trial Batch 12.5 mg tablet and Miles Production Batch 12.5 mg tablet.

PK Parameter	Orudis [®] 25 mg	Miles 12.5 mg Clinical	Miles 12.5 mg Production	90% CI Orudis [®] vs Clinical [#]	90% CI Production vs Clinical [#]
AUC _{0-inf} (ng*hr/mL)	3890 ± 710	1906 ± 312	1900 ± 362	100 - 106	98 - 104
Cmax (ng/mL)	1770 ± 539	847 ± 247	912 ± 216	92 - 116	97 - 122
MRT (hour)	2.60 ± 0.59	2.37 ± 0.36	2.24 ± 0.44	104-119	89-104

[#] The 90% confidence interval acceptance criteria for Ln transformed Cmax and AUC is 80-125%. The 25 mg dose were normalized to the 12.5 mg dose prior to ANOVA.

The phenomena of double peaking is more prominent following the 25 mg ketoprofen dose than the 12.5 mg dose. Individual plasma profiles showed double peaking in 13 out of 30 subjects for Orudis[®], 25 mg dose, 3 out 30 subjects for the 12.5 mg clinical batch and 1 out of

30 subjects for the 12.5 mg production scale tablets. This has been observed by other investigators in other ketoprofen studies. Figure 1 (page 5) represents a sample of individual ketoprofen plasma profiles which demonstrate the double peak phenomena. The mean plasma ketoprofen concentrations for each of the dose levels administered when plotted displayed a smooth rise to a single concentration peak between 1 and 1.5 hours and do not demonstrate the two peak phenomena as displayed in Figure 2 (page 5). Due to the multiple peaks in many of the plasma profiles, mean residence time (MRT) was calculated for each of the treatment groups. MRT represents the average time a drug molecule resided in the body which includes systemic residence as well as residence of the gastrointestinal tract. Assuming systemic clearance is the same for all treatments, any difference in MRT by treatment may be the result to the differences in the residence time in the gastrointestinal tract. Comparisons of the MRT values for the two Miles 12.5 mg tablets show no significance difference. The mean MRT values for the clinical and production scale tablets were 2.37 hours and 2.24 hours, respectively, with a 90% confidence interval ratio of 88.67% to 103.8%. This would support the conclusion that the two Miles tablets provide ketoprofen to the systemic circulation at the same overall rate. The 25 mg Orudis^R capsule had a higher mean MRT of 2.6 hour and falls within the acceptable confidence limits. The company explanation for the higher MRT mean value for the 25 mg capsule is "the greater MRT is observed to correlate with higher doses and is probably related to the flip-flop model for absorption". This reviewer would most likely believe that due to the chemical properties of ketoprofen (pKa = 5.9) there appears to be a double input rate for some individuals. Ketoprofen in some individuals is most likely absorbed in both the stomach and intestinal tract. The tablet is dissolved in the stomach where some ketoprofen is absorbed, but, due to relatively low solubility, some of the ketoprofen precipitates and then is redissolved in the intestinal tract where the rest is absorbed. This would produce two ketoprofen concentration time peaks. Thus, the double peaks are characteristic of the dissolution-gastric emptying kinetics for ketoprofen. Overall, the data supports the conclusion that the plasma concentration for ketoprofen peaks early and is mostly eliminated by 6 hours.

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Figure 1: Individual plasma ketoprofen concentration versus time profiles.

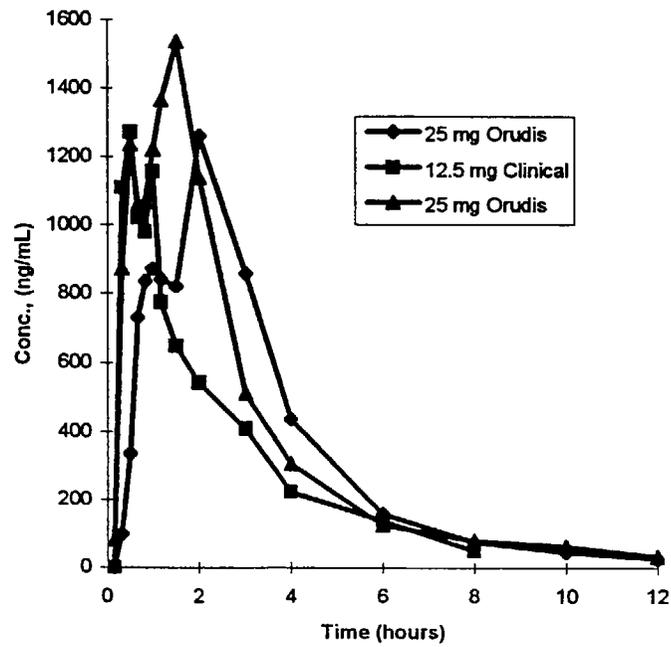
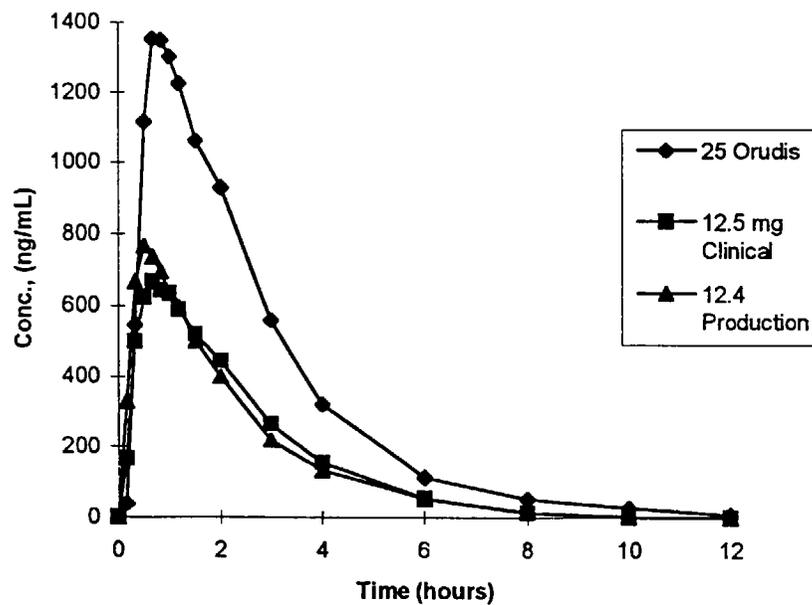


Figure 2: Mean Plasma Ketoprofen Concentration Profiles for 25 mg Orudis^R, 12.5 Miles Clinical Batch and 12.5 Miles Production Batch.



III. PHARMACOKINETICS

A. Background:

Ketoprofen is currently available in the United States in higher immediate release strengths (25, 50, 75 mg) than what Miles is proposing for OTC, the 12.5 mg tablet. There are quite a number of publications on ketoprofen pharmacokinetics. Peter Lockwood, MSc., in his review of NDA 19-816 (Oruvail^R 200 mg slow release tablets) and the Sponsor in this submission, NDA 20-499 did a review of the ketoprofen literature. The following indented paragraphs are a combined pharmacokinetic summary of published ketoprofen (immediate release dosage forms) from both their reviews. *Italic* words are new information added to the summary pharmacokinetics based on information obtained from this NDA.

Absorption

The absorption of ketoprofen is rapid and nearly complete after oral administration, with T_{max} falling between 0.5 and 2 hours. C_{max} varies linearly with oral doses between 3.125 mg and 200 mg. Food reduces C_{max} , extends T_{max} and has no effect on AUC (Jamali & Brocks, 1990).

Plasma protein binding

Ketoprofen is extensively bound to plasma proteins (>99% at therapeutic concentrations) mainly to the albumin fraction, consequently, ketoprofen exhibits a small volume of distribution (0.1 - 0.2 L/kg) (Royer et al., 1986).

Excretion and Metabolism

Ketoprofen is metabolized into inactive ester and ether glucuronide conjugates. In healthy volunteers, practically no ketoprofen is excreted unchanged into bile or urine, however, significant amounts of the ester glucuronide (S more prevalent than R) have been found in the plasma of some elderly subjects with normal age adjusted renal clearance. The cumulative percent of ketoprofen (free and conjugated) excreted in the urine in 48 hours after a single dose 50 mg oral dose was 75.7%, of which approximately 90% was ketoprofen glucuronide (Ishizaki, 1980). It has been reported that the ester (acyl) glucuronide, is unstable and is hydrolyzed to release parent drug during storage, even under freezing conditions. The reasons underlying the greater prevalence of conjugated ester glucuronide in the plasma samples of elderly patients is unclear (Foster et al., 1988). The ether glucuronide is stable and excreted .

Ketoprofen elimination from plasma is rapid, with a half-life ranging from 1 to 3 hours. Following IV administration of ketoprofen, the clearance was estimated to be 5.1 L/hr. Most studies have shown that there is little or no accumulation upon multiple dosing (Foster et al., 1988), With more sensitive assays it has been shown that the ketoprofen half life may range from 18-40 hrs and may be indicative of deep tissue

distribution of ketoprofen (Delbarre et al., 1976). Ketoprofen demonstrates dose-proportional pharmacokinetics within the 3.125 mg to 200 mg dosage range.

The effect of age and disease

The pharmacokinetics of ketoprofen appear to be similar in subjects aged 5 to adult (Lempiainen and Makela, 1987). Higher concentrations of the acyl glucuronide metabolite of ketoprofen have been measured in plasma samples from elderly compared with young subjects. A reduction in renal excretion with age may explain this finding (Verbeeck et al., 1979, Lin et al., 1986). The elderly exhibit a similar rate and extent of absorption of ketoprofen immediate release products. Arthritis patients have similar pharmacokinetics to that of normal subjects when matched for weight and age.

Chronopharmacokinetics

Higher ketoprofen concentrations are observed after AM than PM dosing. Explanations for this observation include decreased absorption at night, increased renal clearance and increased formation of the glucuronide at night. None of these hypotheses have been proven.

Models

Immediate release ketoprofen has been modeled using one and two compartment models with first and zero order absorption. Upton et al. (1981) argues that less than optimum sampling schedules in many of the earlier investigations provided only 3 to 5 points after the peak to a maximum of 12 hours, which inappropriately suggested the kinetics followed a one compartment model. In Upton's study, plasma samples were collected to 24 hours and fitted with a two compartment model with zero order input. However the evidence that the terminal log linear phase had been reached at 24 hours was not strong. The two compartment model was chosen by Upton, because it provided more superior fits as judged by eye and the Akaike criterion.

Oral Bioavailability:

Despite the availability of an IV formulation of ketoprofen the absolute bioavailability of oral ketoprofen preparations has not been reported. Using AUC values reported in different studies, Jamali and Brocks (1990) calculated the absolute bioavailability of ketoprofen to be > 92%. (Reviewer's comment: This is in good agreement with what is known about the excretion of ketoprofen. As mentioned, in the Excretion and Metabolism Section of this review, 90% of a single oral ketoprofen dose was eliminated as ketoprofen glucuronide.) *Study 0284 demonstrated that the absolute bioavailabilities for the R-enantiomer were 77.9%, 79.2% and 82.3% and for the S-enantiomer, 68.2%, 74.2% and 79.7% for the 12.5 mg, 25 mg and 50 mg oral tablet, respectively.*

Accumulation:

Upton (1981) reports that there was about 20% accumulation after multiple dosing (every 6 hours for 13 doses) of 50 mg immediate release ketoprofen.

Maximum plasma concentrations at steady state

Peak levels at steady state are linearly related to the dosage regimen. Jamali and Foster (1990) report a number of studies where C_{max} ranged after a 50 mg dose, 10.1 ug/ml after a 100 mg dose, after a 150 mg dose and after a 200 mg dose.

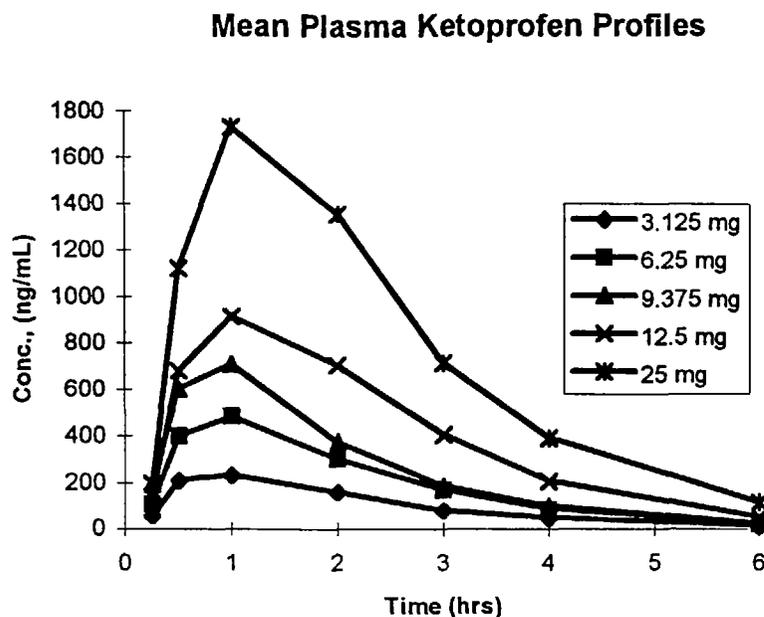
B. Dose Proportionality:

After single oral ketoprofen doses ranging from 3.125 mg to 25 mg, bioavailability and clearance remain independent of dose.

A secondary objective of Study S90-2 (page 40) was to assess the dose proportionality of the pharmacokinetics in a patient population. The protocol was designed as a double-blind placebo controlled study of randomized parallel groups with five primary groups of 35 subjects for the analgesic efficacy portion two supplementary groups of 10 subjects added for the pharmacokinetic-pharmacodynamic (PK-PD) aspects. The patient population was female and male Puerto Rican dental patients undergoing the surgical removal of 1 or more third molar dental impactions. The assessment of dose proportionality included the 3.125 mg tablet (n=10), 6.25 mg tablet (n=33), 9.375 mg tablet (n=10), 12.5 mg tablet (n=35) and the 25 mg tablet (n=34). Figure 3 on the next page presents the mean plasma ketoprofen concentrations for each of the dose levels administered. While these plots indicate a smooth rise to a single concentration peak between 1 and 1.5 hours, examination of the data for each individual patient show most to have two peaks. To curve-fit the data for each patient required a two lag-time and two input mathematical model. Overall, the data supports the conclusion that the plasma concentration for ketoprofen is proportional to dose and that the concentration peaks early and are mostly eliminated by 6 hours.

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Figure 3: Mean plasma ketoprofen profiles for the 3.125 mg tablet (n=10), 6.25 mg tablet (n=33), 9.375 mg tablet (n=10), 12.5 mg tablet (n=35) and the 25 mg tablet (n=34).



Further, plots which present the linear regression for peak concentration and AUC_{0-inf} (as normalized to a 70 Kg patient) versus the dose of ketoprofen are located in the detailed summary report for Study S90-2 in the Appendices. The data is consistent with the plasma concentrations being directly proportional to the dose administered. The data estimated the apparent oral clearance (CL/F) of about 5.5 L/hour. The estimated terminal half-lives are essentially identical for all dose levels at about 1 hour.

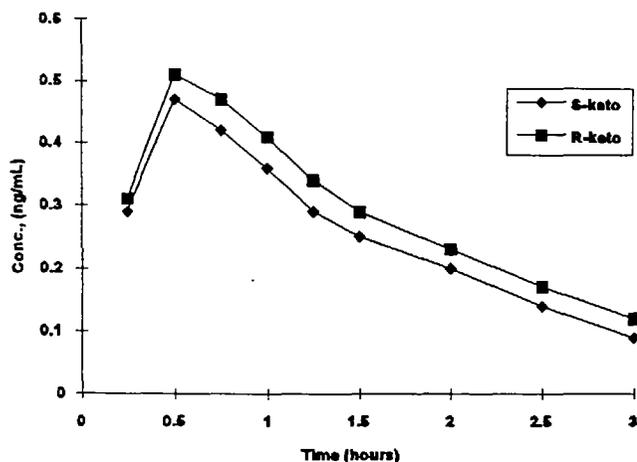
C. Enantiomers:

Ketoprofen is marketed as a racemate with the S-enantiomer possessing beneficial pharmacological activity. The enantiomers demonstrate similar concentration-time curves. They do not appear to compete for elimination and their distribution is similar. Absorption is not stereoselective. About 10% of the R enantiomer is inverted to S-ketoprofen in human plasma after oral administration (Foster & Jamali, 1988).

Study 0284 (page 48) was an open-label study in healthy male and female volunteers (n=12, n=12). Four oral doses of ketoprofen (6.25, 12, 25, 50 mg) and an intravenous dose (50 mg) were given to the volunteers to determine the pharmacokinetic characteristics of the two enantiomers after the racemic form was administered at different doses. With respect to

AUC_{0-inf} , dose linearity was found for both enantiomers of ketoprofen in the 6.25 to 50 mg dose range. The bioavailability of all the ketoprofen doses is lower after oral administration than after intravenous administration. The normalized AUC values calculated for the respective doses demonstrate that, compared with intravenous administration, only 65% to 85% of the administered dose was bioavailable for oral ketoprofen. The absolute bioavailabilities for the R-enantiomer were 77.9%, 79.2% and 82.3% and for the S-enantiomer, 68.2%, 74.2% and 79.7% for the 12.5 mg, 25 mg and 50 mg oral tablet, respectively. This slight reduction in bioavailability in comparison with intravenous administration may be explained by incomplete absorption and by slight presystemic metabolism. The pharmacokinetic parameters, C_{max} , T_{max} (12.5, 25 mg), AUC, CL and V_{ss} after oral administration and AUC and CL after intravenous administration were found to differ from each other to a significant extent ($p < 0.05$). The values for C_{max} and AUC are smaller for S-ketoprofen than for the R-enantiomer. The volumes of distribution and the clearance are consequently greater for the S-enantiomer. It may be conjectured that the slight reduction in bioavailability for S-ketoprofen is due to a higher presystemic clearance of the S-enantiomer. Figure 4 on the next page presents the mean plasma ketoprofen profiles for both enantiomers at the 12.5 mg dose. The other doses have similar time versus concentration profiles for the enantiomers but at higher concentrations.

Figure 4: Mean R and S-Ketoprofen Plasma Profiles After a 12.5 mg Racemic Oral Dose Of Ketoprofen.



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D. Gender: *There appears to be no difference in pharmacokinetic parameters between men or women.*

Study 0284 (page 48) was a non-blind study in healthy male (n=12) and female (n=12) volunteers that aged in range from 22-40 years. There were no statistical differences in AUC_{0-inf} , C_{max} or F between the sexes. Whether gender differences existed or not was not reported in the previous ketoprofen NDA's (NDA 18-754 or NDA 19-816) or in the current labeling of these products.

E. Pharmacodynamics:

Data from Study S90-2 (page 40), "A Comparative Analgesic Efficacy Study of Ketoprofen vs. Ibuprofen and Placebo in Postsurgical Dental Pain With Pharmacodynamic and Pharmacokinetic Evaluation," were analyzed with the primary objective to estimate the concentration-response relationship of ketoprofen. A few comments by this reviewer are necessary to state why a detailed validation of this study was not done. First, this study does not impact on the approvability of this NDA from a pharmacokinetic standpoint. Higher prescription ketoprofen doses are already approved, pharmacokinetics, efficacy and safety have been established. Finally, the results from this study will not add any new information to the labeling. The main studies for approvability for an OTC switch from a pharmacokinetic standpoint, are the bioequivalency between the clinical capsule and the proposed 'to-be-marketed' tablet and dose proportionality between the 12.5 mg and 25 mg ketoprofen dose. However, a brief description of the study design and pharmacokinetic results will be described in the next paragraph. The results of the pharmacodynamic portion are of interest to this reviewer, but the methodology is under development and needs further validation. Briefly, a logistic model was used to estimate the cumulative distribution function of observing a Pain Relief (PR) score, a discrete variable. Using Maximum Likelihood estimates, the expectation of PR score could be calculated at a given time for a given dose. The pharmacodynamic model used currently does not create data for responses after subjects discontinue the study. The new methodology seems to be appropriate to these data because it recognizes their categorical nature. No further discussion or presentation of pharmacodynamic results will be presented in this review. However, the pharmacokinetic parameters obtained from this study will be presented.

Study S90-2 (page 40) had two primary objectives; 1) to assess the analgesic efficacy and onset of meaningful pain relief of ketoprofen (6.25 mg, 12.5 mg and 25 mg) compared to ibuprofen 200 mg and placebo following a single oral dose in patients with post surgical dental pain and 2) to estimate the PK-PD curves of ketoprofen in a study population of patients with post-surgical dental pain. The design is described in B. Dose-Proportionality Section of this review. A total of 175 patients undergoing the surgical removal of 1 or more third molar dental impactions were randomized into five treatment groups were included in the efficacy

analysis. Ketoprofen 6.25 mg, 12.5 mg and 25 mg, and ibuprofen 200 mg were all found to be effective analgesics when compared to placebo. The two higher doses of ketoprofen (12.5 and 25 mg) provided similar analgesia, indicating a plateau effect between the two dosage levels. The ketoprofen 12.5 and 25 mg doses provided greater relief than ibuprofen at some of the early time points, with a significantly faster onset of effect. Ibuprofen 200 mg demonstrated a longer time to offset than ketoprofen. These observations are consistent with the pharmacokinetic profiles for both drugs. Ketoprofen is absorbed earlier but has a shorter mean residence time than ibuprofen. The pharmacokinetic model that described the data was a two-compartment open model with first-order absorption, and an absorption lag time. The final pharmacokinetic parameter estimates in the typical individual and their interindividual variability are shown in Table 2.

Table 2: Final pharmacokinetic parameter estimates in the typical individual and their interindividual variability following either a single 3.125 mg, 6.25 mg, 9.375 mg, 12.5 mg or 25 mg ketoprofen capsule dose.

Parameters	Mean	95% Confidence Interval of Mean	Interindividual Variability (CV%)
k ₂₁ (h ⁻¹)	0.316	(0.112, 0.520)	10.2
V/F (L)	7.02	(5.93, 8.09)	33.7
CL/F (L/h)	5.24	(1.30, 8.18)	58.1
k _a (h ⁻¹)	2.40	(1.85, 2.99)	27.5
alpha (h ⁻¹)	0.955	(0.731, 1.179)	---
Beta (h ⁻¹)	0.247	0.110, 0.384)	---
t lag (h)	0.222	(0.181, 0.263)	2.0

IV. DISSOLUTION

As of this date, there is no official dissolution specification set in the U.S. Pharmacopeia National Formulary for Ketoprofen. The Sponsor performed dissolution testing according to the USP paddle method (1000 mL) at pH 7.4 phosphate buffer and 50 rpm. Six dosage units per batch were tested. Four (4) full scale production batches were tested and the dissolution specification, if set, would be The dissolution means on the four production batches for percent dissolved

The dissolution specification for ketoprofen tablets would meet the original recommendation made by the USP for capsules (Q = 70% in 30 minutes). However, this reviewer would recommend the following dissolution method and

specification for ketoprofen tablets:

In addition to this review, this reviewer is also reviewing another NDA for 12.5 mg OTC ketoprofen tablets/caplets (NDA 20-429) in which the dissolution specification would need to be set at $\geq 80\%$ at 30 minutes. Setting the above recommended dissolution method and specification would support both the capsules (Orudis[®]) and 12.5 OTC tablets/caplets dissolution data. Appendix IV (page 56) contains the dissolution profiles of the four full scale production batches tested.

V. ANALYTICAL

Plasma concentrations of racemic ketoprofen were determined

The assay method and its specific application to the studies is acceptable.

Sensitivity:

Accuracy:

Precision:

VI. STUDY CONCLUSIONS

From the studies submitted in support of this NDA (20-499), the Sponsor has adequately described the pharmacokinetics of the 12.5 mg ketoprofen tablet/caplet. In particular, the Sponsor has demonstrated the following:

1. Bioequivalence: Study S91-005 supported that the clinical batch was bioequivalent to the production batch (AUC and C_{max} were within the bioequivalence criteria of 80-125% for ln transformed data).

2. Dose Proportionality: Study S90-2 supported that after administering single oral ketoprofen doses ranging from 3.125 mg to 25 mg, bioavailability and clearance remain independent of dose.

3. Enantiomers: Ketoprofen exhibits only a limited extent of stereoselectivity in its pharmacokinetics and therefore data generated using nonstereospecific approaches can be extrapolated to predict the pharmacokinetics of individual enantiomers.

4. Dissolution: As of this date, there is no official dissolution specification set in the U.S. Pharmacopeia National Formulary for Ketoprofen. Four (4) full scale production batches were tested and the dissolution specification, if set, The dissolution specification for ketoprofen tablets would meet the original recommendation made by the USP for ketoprofen capsules (Q= 70% in 30 minutes). This reviewer would recommend the following dissolution method and specification for ketoprofen tablets and capsules (see Dissolution Section for further reasoning):

Ruth E. Stevens, Ph.D.

Senior Pharmacokineticist
Pilot Drug Evaluation Staff

Ph.D.
5-25-95

Peer Reviewer, E. Dennis Bashaw, Pharm.D. _____ 5/25/95

Biopharmaceutics Day (5/24/95), Ludden, Malinowski, Fleischer, Hepp, Gillespie, Hussain, Bashaw and Stevens

cc.

- HFD 007 Original NDA 20-499 (X1)
- HFD 007 CSO (Morgan) (X1)
- HFD 007 Stevens, PK files (X2)
- HFD 426 (Fleischer) (X1)
- HFD 427 (Chen) (X1)
- HFD 420 (Chron., Drug, Reviewer) (X3)
- HFD 19 (FOI) (X1)
- HFD 344 (Viswanathan) (X1)