CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Bromfenac Sodium Capsules
25 and 50mg
NDA 20-535
Reviewer: E.D. Bashaw, Pharm.D.
APW

Wyeth-Ayerst Laboratories
Philadelphia, PA 19101

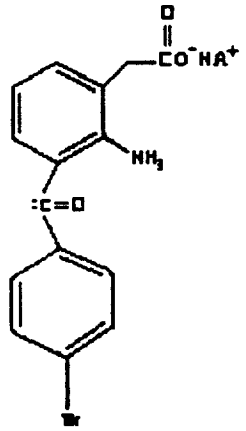
Submission Date:
30-Dec.-1994

Review of an NDA

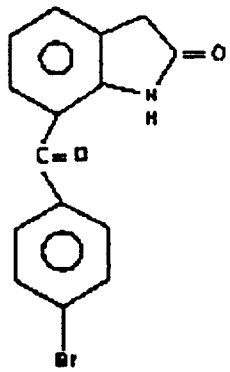
I. Background

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID). As such the sponsor is seeking approval of this NDA for use in the management of acute and chronic pain, including the pain of osteoarthritis and primary dysmenorrhea at doses of 25-50mg q8-12 hrs. The IND for bromfenac was originally submitted to the FDA by A.H. Robins in July 1984. After the corporate acquisition of A.H. Robins by American Home Products, the bromfenac sodium IND was transferred to Wyeth-Ayerst Laboratories in May 1990. At the present time the Agency and the sponsor have not been able to agree on a tradename for this product.

Chemically bromfenac sodium is 2-amino-3-(4-bromobenzoyl)-monosodium-salt. It is a yellow to orange crystalline solid that is freely soluble in water. A saturated solution of bromfenac sodium has a pH of 9.5. The pKa of the drug is 4.3. Bromfenac sodium is achiral. In acid conditions bromfenac undergoes a cyclization reaction to form AHR-10240.



Bromfenac



AHR-10240

Besides being a degredant, AHR-10240 is the primary metabolite of bromfenac detected in the urine. Bromfenac has not been marketed or introduced in any country.

II. Recommendation

In this NDA the sponsor has submitted the results of over 20 in vivo pharmacokinetic studies. Bromfenac has been studied in both males and females, young and elderly. Single and multiple dose pharmacokinetic studies have been done to demonstrate dose proportionality over the range of doses from 5 to 100mg. The effect of food has also been

exhaustively tested on the final dosage form, as has the effects of both renal and hepatic insufficiency. The sponsor has conducted numerous drug interaction studies including studies with methotrexate, cimetidine, warfarin, and digoxin. The sponsor has also demonstrated in vivo bioequivalency between the to-be-marketed capsule and experimental capsules used in the clinical program. From a biopharmaceutic perspective the NDA is approvable, provided final language for the label that is mutually acceptable can be worked out.

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Appendix I-Study Summary Sheets

In Vivo-Pivotal Studies

Supportive Studies-PK

III. Application Overview

The pharmacokinetic portion of this NDA (section 6) consists of 95 volumes of data (volumes 1.49-1.144). In this material are the results of 25 in vivo biopharmaceutic studies involving approximately 1000 subjects (352 healthy volunteers, 647 patients). Because of the mass of data this represents the sponsor provided an electronic copy of the data on a laptop computer.

Of the total number of studies submitted ten were considered by this reviewer to be pivotal and six were considered to be supportive. The remaining nine studies are not included in this review as they represent either dosage forms that were not developed or they were replaced by other trials using the final dosage form or with a larger number of subjects. For these reasons they were not considered to be relevant for approval and were not included in the final review of the product.

A. Analytical (vol. 1.56)

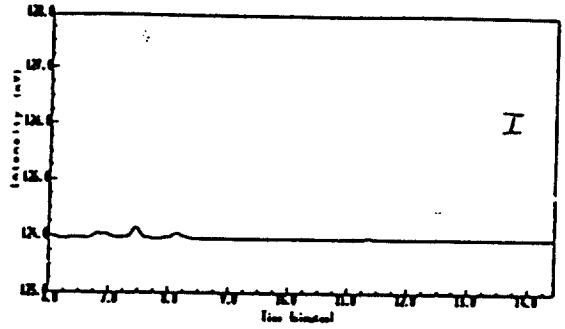
During the development of bromfenac biological samples of plasma, whole blood, and urine were analyzed for bromfenac and its metabolites. Analysis of biological samples for bromfenac were conducted either by Wyeth-Ayerst Research (W-AR, Princeton, N.J.), or for the studies conducted by A.H. Robins, at A.H. Robins Company (Richmond, Va.). For the purposes of this review only the validation of the W-AR and sites will be described.

The analytical procedure used in this trial at both analytical sites was similar for both plasma and urine samples. Briefly,

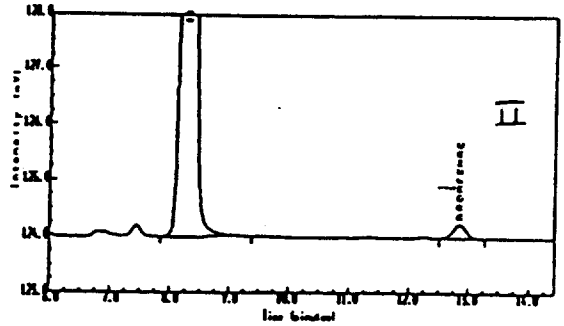
Reproduced below are four representative chromatorgrams from this NDA.

Chromatogram

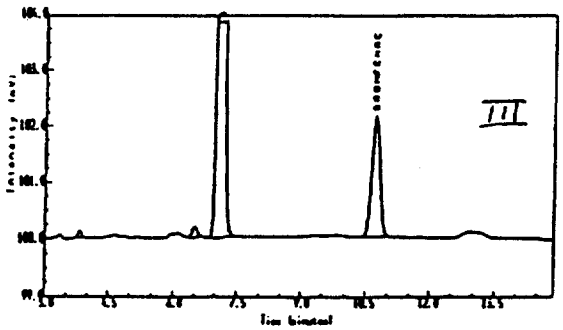
I. Plasma blank
II. 30ng/ml limit of detection (from validation report)
III. Random subject chromatogram (Study #116. Subject #1, Day 8, Hour 6, representing 364ng/ml.)
IV. 30ng/ml standard from Study #116.



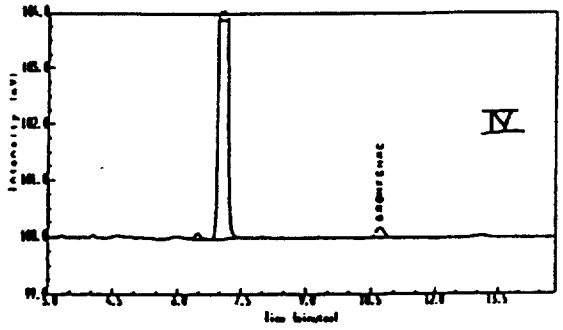
Analyst Name : JEC
Line Id :
Comment :
Method Title : HARS2015V
Sample Name : PLASMA BLANK
Sample Id :
Sample Type : Sample Amount=1.00000
Bottle No : 10



Analyst Name : JEC
Line Id :
Comment :
Method Title : HARS2015V
Sample Name : STD 30.0
Sample Id :
Sample Type : Standard Amount=1.00000
Bottle No : 9



Analyst Name : SM/KG
Line Id :
Comment : S:SUBJECT, D:DAY, H:HOUR, M:MINUTE, L:LEG
Method Title : SET01
Sample Name : S 01 D 8 H 6.0
Sample Id :
Sample Type : Sample Amount=1.0000
Bottle No : 12



Analyst Name : SM/KG
Line Id :
Comment : S:SUBJECT, D:DAY, H:HOUR, M:MINUTE, L:LEG
Method Title : SET01
Sample Name : *STD 30.0 NG/ML
Sample Id :
Sample Type : Standard Amount=1.0000
Bottle No : 28

Examination of the chromatograms provided by the sponsor reveals no interfering substances and good separtion of internal standard from the target peak. There is some movement present in the elution time of the target peak, but this does not appear to be severe and represents normal operation.

Accompanying each of the study summary reports in Appendix I is a brief summary of the performance of the assay during each study. In addition to the normal assay validation reports, the sponsor included with each report 10% of the chromatograms obtained

during each trial. At this reviewers direction this was done by selecting 10% of the subjects, rather than a random sampling of 10% of the total number of generated chromatograms. These chromatograms were visually inspected (at random) by the reviewer for evidence of an unstable baseline and interfering substances. No problems were noted by this reviewer.

All in all the sponsor presented acceptable analytical documentation on the performance of the assay for each of the pivotal studies. For some of the earlier studies the documentation was somewhat scant, but as these studies were not included in the final evaluation of the dosage form, no harm was done.

B. Formulation

At the present time the sponsor is pursuing a 25 and 50mg capsule for marketing. A 100mg capsule was also used in clinical trials but was not developed for marketing. As was noted in the background section of this review A.H. Robins was the original developer of bromfenac. When Wyeth-Ayerst took the project over they initiated new trials with their own formulation. At this time none of th A. H. Robins work has been included in this review as the Robins data has been superseded by new data from Wyeth.

During the clinical development of this product, bromfenac was produced in a Wyeth-Ayerst facility at Montreal, Canada. Upon approval manufacturing will be transferred to another Wyeth-Ayerst facility in Guayama, Puerto Rico. To facilitate the move the sponsor has included in this NDA an in vivo bioequivalency study of the two sites. The final clinical batches were made at the Guayama, Puerto Rico site.

Active Ingredients:	25mg	50mg
Bromfenac Sodium*	28.67	57.34
Inactive Ingredients:	-	-
Silicon Dioxide, Colloidal, NF		
Lactose Monohydrate, NF		
Magnesium Stearate, NF		
Hard Gelatin Capsule #4 (lt. yellow body, opaque red cap).		
Hard Gelatin Capsule #3 (opaque orange body, opaque red cap)		
Total Capsule Weight:		

IV. Summary of Bio/PK characteristics

A. Metabolism (792-A-102-US).

The metabolic fate of bromfenac was investigated in six healthy adult males in study 792-A-102-US. Each subject was dosed with a 50mg dose of bromfenac that was radiolabeled with 50uci of ^{14}C. Blood, urine and feces was collected over 96 hours. Results from this study indicated that bromfenac is well absorbed with ~80% of the labeled dose appearing in

the urine (66% appearing in the urine in the first 8 hours). Summary results of this trial are reproduced below, detailed results for each individual are attached in Appendix I as pages 2-4.

Percent of Radioactivity Recovered					
	Day 1	Day 2	Day 3	Day 4	Total
Urine	78.6	2.9	0.6	0.2	82.4
Feces	1.54	4.51	7.78	0.52	13.22
Total	80.14	7.41	8.38	0.72	95.6

Two subjects, #1 and 5 were excluded from the calculation of recovered radioactivity as recovery was low in subject #1 (48%) and high in subject #5 (105%). Investigation of the data from these two subjects in this trial suggested that sample handling procedures were to blame. While this is a plausible explanation it is not a definitive one, however, as the primary goal of this study was to identify routes of elimination and not to establish definitive final parameter values, their explanation is acceptable.

Analysis of the plasma revealed that bromfenac was the only circulating species present in the blood up until the later time points when a small, unquantifiable, metabolite peak was detected in a couple of the subjects plasma. The whole blood:plasma ratio of radioactivity averaged 0.2, suggesting only slight uptake into formed blood products. Non-compartmental pharmacokinetics were done on the individuals and a mean half-life of 4.54 hrs. was determined for the radiolabel.

Analysis of the urine and fecal material indicated that bromfenac is extensively metabolized. No free bromfenac or bromfenac conjugates were found in the urine. The primary metabolite appeared to be a cyclic amide of bromfenac (also know as AHR-10240, see page 1). In addition 4 minor metabolites, possible glycone conjugates, were also detected but not identified in the urine.

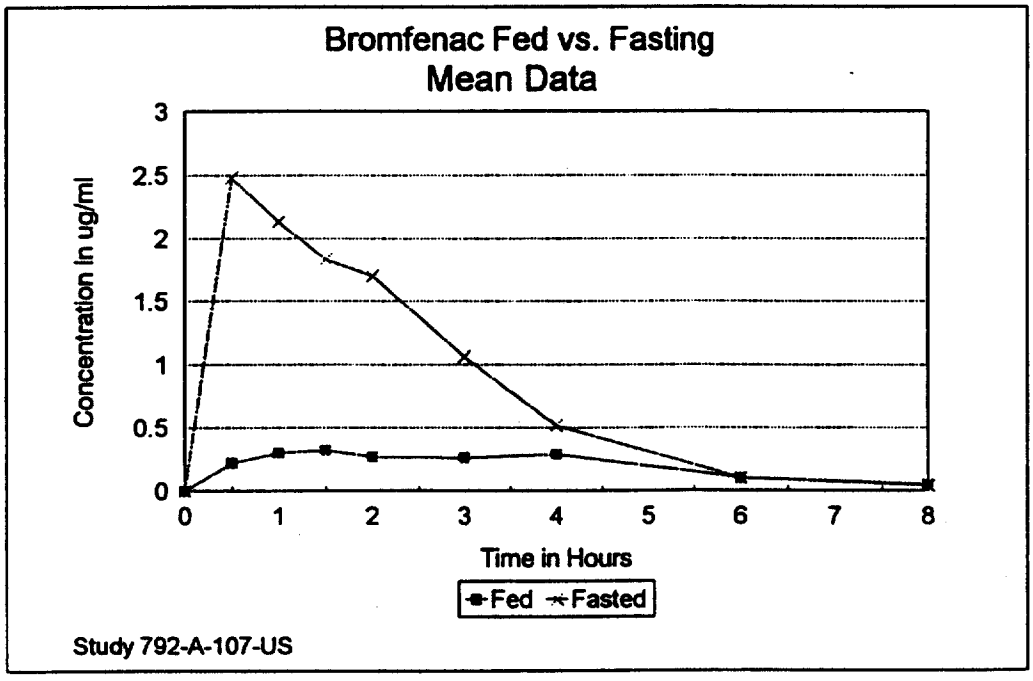
In conclusion, this study demonstrated that bromfenac is well absorbed and rapidly metabolized and excreted in the urine. Bromfenac is most likely the active therapeutic moiety as analysis of the circulating plasma did not detect any circulating metabolites until late in the plasma profile.

B. Absolute Bioavailability & Food (792-A-107-US)

While the previous study demonstrated that bromfenac itself is well absorbed from an experimental capsule, the sponsor also investigate the absolute bioavailability of the final to-be-marketed dosage form. This study involved the comparison of a single 50mg dose of bromfenac, in market image capsules, to 50mg of bromfenac administered intravenously. In addition, each subject received each treatment in a fed (FDA high fat breakfast) or fasting condition to assess the effect of food on bioavailability. A total of 24 subjects were enrolled in this trial (23 males, 1 female) and all subjects completed this trial. Reproduced below are the summary results from this trial, detailed results are attached in Appendix I as pages 5-9.

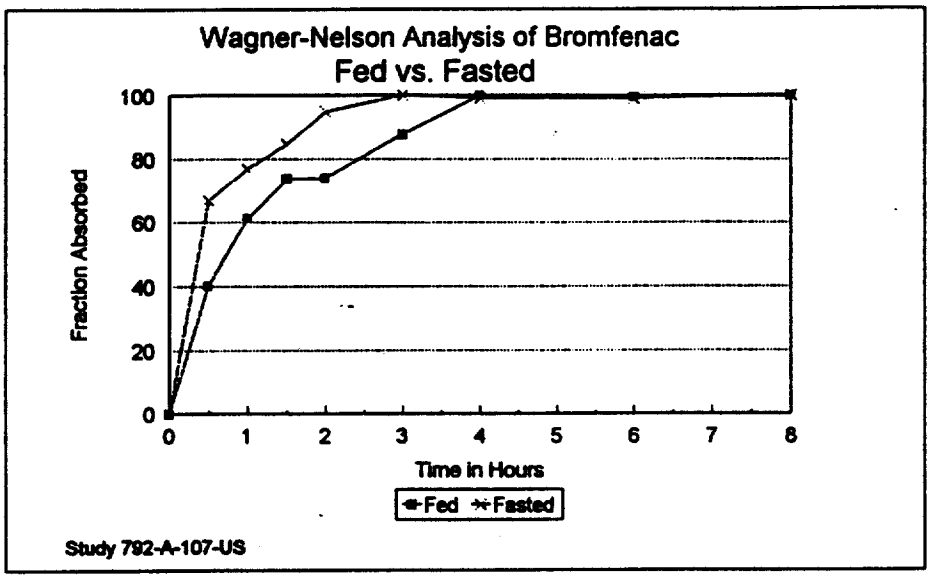
Absolute Bioavilability Under Fed/Fasting Conditions Mean+/-S.D.				
	Intravenous		Oral	
	Fasting	Fed	Fasting	Fed
F%	100+/-0	100+/-0	67+/-20	27+/-14
AUC(mg*h/L)	9.7+/-3.0	7+/-2.4	6.5+/-2.7	1.7+/-1.0
Cmax(mg/L)	11.6+/-3.1	11.2+/-2.1	3.3+/-1.4	0.6+/-0.5
Tmax(hrs)	0.09+/-0.03	0.08+/-0	1.35+/-0.87	2.79+/-1.85
T1/2(hrs)	2.5+/-1.1	2.0+/-1.2	1.7+/-1.1	1.6+/-0.8

The results of this study clearly suggest that bromfenac is not very bioavailable. With a fasting bioavailability of only 67%, compared to 80% in the radiolabeled study, it would appear that either the formulation chosen for clinical development and marketing was not optimized for drug delivery or that formation of bromfenac's degradation product AHR-10240 is very rapid in the stomach. As for the effect of food it is apparent that co-administration with food, a common recommendation with most NSAID's, would significantly reduce the activity of this dosage form. A comparison of mean plasma levels clearly demonstrates the problem:



With the nearly 80% reduction in peak plasma levels and a 75% reduction in total area under the curve it appears unlikely that bromfenac administered under such circumstances would be clinically useful. In a clinical study (792-A-311-US) the sponsor gave subjects under going dental extraction various doses of bromfenac from 5 to 200mg. The results of this trial suggested that the 5mg dose was an effective analgesic but that the time to re-medication was reduced relative to the higher doses. This study will be discussed further in its own sub-section.

As for the general pharmacokinetic performance of this product, the dosage form is rapidly absorbed under fasted conditions with peak plasma levels occurring within 90 minutes of dosing. Analysis of the fraction absorption data via Wagner-Nelson methods by this reviewer shows a rapid absorption profile with ~70% of the bioavailable dose absorbed after only 30minutes. Interestingly, a similar analysis of the fed data reveals that while the bioavailability of the dosage form may be reduced, what is absorbed is done so rather rapidly.



The most notable finding from this study, besides the reduced bioavailability, is the reduction in plasma half-life in comparison to the half-life determined in the radiolabeled study. In this study all four treatments gave estimates of half-life approximating 2 hours. This is in sharp contrast to the 4.5 hour half-life from the previous study. This discrepancy is most likely due to loss of the radiolabel in the body, the possibility of other undetected longer half-lived metabolites (unlikely given the fractional recovery), or the non-specificity of the radiolabel methods. In any event the reproducibility of the two hour half-life in this study clearly indicates that bromfenac will have to be dosed frequently to be effective, as by 8 hours after dosing plasma levels dropped in this study to below detectable limits (<30ng/ml). Given this half-life it is most likely that bromfenac will require either qid or tid dosing to be effective.

A peculiarity of the data from this study is the effect of food on intravenous dosing. Under fed conditions the total AUC of the intravenous dose is decreased approximately 30%, relative to that of the fasted intravenous treatment. There is no effect on the peak plasma levels, but the terminal half-life is also shorter by approximately 1/2 hour. The meaning of this is unclear. A possible explanation is that as bromfenac is highly extracted and liver blood flow dependent, the increase in liver blood flow caused by a meal would result in a transient increase in bromfenac clearance. While other mechanisms are possible, this transient effect on liver blood flow seems to be the best fit to the observed data.

As a secondary objective of this trial was to examine the protein binding of bromfenac of a range of clinically relevant concentrations. Using equilibrium dialysis with [^{14}C]bromfenac as a radioactive tracer. The results of these test showed that bromfenac, like most other NSAID's is a highly protein drug with a mean fraction unbound of only 0.12%.

All in all this study has demonstrated that bromfenac, in the market-image capsule, is rapidly yet incompletely absorbed with a fasted absolute bioavailability of only 67%. Food significantly decreases the absolute bioavailability of bromfenac to only 24%. The observed plasma half-life of bromfenac was approximately 2 hours intravenously and 1.5 hours orally. Throughout the trial the only species detected in the plasma was bromfenac and in the urine neither unchanged bromfenac or its glucuronides was detected.

C. Dose Proportionality (792-A-105-US)

As most NSAID's are indicated for chronic therapy the single dose performance of the bromfenac capsule is of limited interest to the clinician. Given the observed plasma half-life of approximately 1.5 hrs. after oral dosing it is unlikely that any significant accumulation will result with more than every four hour dosing. From clinical studies the duration of action of bromfenac has been estimated in pain models to be approximately 6-8 hours. At the present time the sponsor is proposing an every 8 hours dosing regimen. Given the relatively rapid absorption of bromfenac it is unlikely, given its half-life, that bromfenac will accumulate in the plasma under such conditions.

In order to investigate the degree of accumulation upon multiple dosing and to assess dose proportionality the sponsor undertook a multiple dose study using 26 healthy adult males of whom 24 completed the trial. Two subjects discontinued from the trial for personal reasons and their data was not used in the final analysis. The doses used in this trial included a 5mg experimental capsule, and the market image 25mg capsule dosed in single (25mg), double (50mg), and quadruple (100mg) treatments. In order to minimize the number of treatment legs the study was designed such that each subject would have single dose pharmacokinetics performed following the first dose in the first treatment period. This resulted in a parallel group design with a N=6 for each of the single dose treatment legs. The subjects then continued on to steady-state without additional first day plasma sampling for the other treatments, resulting in a N=24 for the steady state conditions. Presented below in separate sections are the summary results of the single and multiple dose phases of this trial, detailed results are attached as pages 10-17 in Appendix I.

Single Dose

Single Dose Proportionality Mean Data +/- S.D.				
N=6	5mg	25mg	50mg	100mg
AUC(mg*h/L)	0.58+/-0.079	3.29+/-1.46	7.91+/-2.22	12.7+/-5.35
Ratio vs. 25mg	0.17	1	2.4	4.8
Cmax(mg/L)	0.37+/-0.093	1.86+/-0.92	4.61+/-1.27	7.9+/-4.74
Ratio vs. 25mg	0.19	1	2.5	4.3
Tmax(hrs)	0.79+/-64	0.92+/-0.58	0.58+/-0.2	0.58+/-0.2
T1/2(hrs)	0.96+/-0.19	1.13+/-0.37	1.14+/-0.1	1.15+/-0.15

In regards to the demonstration of single dose proportionality, the small number of subjects and parallel group design of the study makes the results somewhat less reliable than one would like. In addition, one is presented with the problem of selecting a reference dose. In this

case the reviewer chose the 25mg capsule as the reference as it is the market-image capsule and the 5mg experimental capsule has never been tested before. If the 5mg capsule was chosen as the reference capsule it is not at all clear that one would be able to properly determine the relationship of one dose to the other as the lack of use of the 5mg capsule makes it an undefined entity.

The data from this single dose phase clearly suggests dose proportionality between the 25, 50, and 100mg dose levels. The deviations noted in the data, i.e. the ratio of 2.4 and 2.5 for the 50mg dose, are most likely due to the variability present in the data. With %CV's of 30-50% for some of the parameters this degree of deviation is not suprising. As the ratio for the 100mg dose is slightly lower than what would be expected this deviation does not appear to be significant. As for the 5mg dose it also appears to be dose proportional in that its ratio to the 25mg capsules approximates the ideal of 0.2.

Multiple Dose

Multiple Dose Proportionality Mean Data +/- S.D.				
N=24	5mg	25mg	50mg	100mg
AUC(mg*h/L)	0.53+/-0.23	2.89+/-0.87	6.14+/-1.75	12.3+/-3.16
Ratio vs. 25mg	0.18	1	2.12	4.25
Cmax(mg/L)	0.37+/-0.15	1.85+/-0.74	3.93+/-1.35	8.24+/-2.96
Ratio vs. 25mg	0.2	1	2.12	4.45
Tmax(hrs)	0.91+/-0.5	0.88+/-0.55	0.67+/-0.26	0.63+/-27
T1/2(hrs)	0.95+/-0.36	1.27+/-0.72	2.14+/-0.85	2.7+/-1.21

As with the single dose portion of this study the 25mg dose was selected as the reference treatment. In this portion of the study it appears that there is an increasing amount of non-linearity, especially as it relates to peak plasma levels. Even so the amount of apparent non-linearity is approximately 10% and appears to be more related to the apparent increase in plasma half-life with dose. The reason for this increase in half-life is most likely due to the prolonged plasma sampling scheme used for the multiple dosing phase of this study. Examination of the plasma profiles suggests that there may be another compartment present in the profile of bromfenac that could be described with higher doses. The impact of this deep compartment seems, however, to be minimal as there was no evidence of significant drug accumulation with repeated doses of bromfenac.

From a statistical point of view, statistically significant differences were detected for Tmax, T1/2, Cl/F, $V\lambda z$, MRT_{oral}, λz, and dose normalized AUC between the four treatments. However, if one excludes the 5mg dosing regimen, statistically significant differences remain only for Tmax, T1/2, $V\lambda z$, and λz. Of these the difference in Tmax is most likely a consequence of discrete sampling times, while the differences detected in λz are due to assay sensitivity at low plasma concentrations. The λz calculated for the 50 and 100mg steady-state data was generally based on plasma concentrations occurring 6 hours or longer after dose administration. In contrast λz for the 25 and 5mg treatments was based on plasma concentrations between 4 and 6 hours. For the lower dosage regimens, the calculated λz might overestimate the true λz (and hence,

underestimateT1/2 and AUC). The statistical differences observed in T1/2 and Vλz are a function of these parameters being directly calculated from λz.

In conclusion, although statistical differences are detectable between the dose normalized treatments, these differences are minimal and are most likely due to the prolonged plasma sampling period afforded by using higher doses of bromfenac. Across a range of doses from 5 to 100mg the sponsor has adequately demonstrated dose proportionality.

D. Age and Gender Effects (792-A-104-US)

Up until this study the majority of the pharmacokinetic work done with bromfenac was done in healthy adult males. This study was designed to evaluate the effect of age and gender on the pharmacokinetics of bromfenac. A total of 44 subjects (see Table II, below) were enrolled in this study.

Sex	Young*	Young-Elderly**	Elderly***
Males (N=22)	10	6	6
Females (N=22)	10	6	6

*Young = 18-45 yrs old
**Young-Elderly = 65-74 yrs old
***Elderly = 75yrs old

All subjects enrolled in this trial received a single 50mg dose on day 1, followed by 50mg every 12 hours for six doses. On study days 1 and 4, plasma and urine samples were collected for 24 hours to measure bromfenac levels. As with the previous multiple dosing study the results from this study will be presented separately. Summarized below are the results from the single dose phase of this study, detailed study results are attached in Appendix I as pages 18-30.

Single Dose

Single Dose Pharmacokinetics of Age and Gender						
	AUC* (mg*h/L)	Cmax* (mg/L)	Tmax (hr.)	T1/2 (hr.)	Cl/F (L/hr/Kg)	Vλz/F (L/Kg)
Young Males	6.9+/-1.9	4.6+/-1.8	0.85+/-0.61	1.2+/-0.4	0.097+/-0.02	0.16+/-0.04
Young Females	10.8+/-2.6	6.2+/-2.5	0.90+/-0.29	1.5+/-0.8	0.083+/-0.02	0.18+/-0.13
Young-Elderly-Males	7.9+/-2.0	4.9+/-2.3	0.71+/-0.19	1.4+/-0.5	0.085+/-0.03	0.16+/-0.04
Young-Elderly-Females	11.4+/-3.5	6.3+/-3.1	1.21+/-0.95	2.1+/-0.9	0.07+/-0.03	0.19+/-0.05
Elderly Males	13.1+/-2.0	7.0+/-1.7	0.58+/-0.13	2.7+/-0.3	0.05+/-0.01	0.19+/-0.02
Elderly Females	16.3+/-5.7	8.9+/-2.6	0.71+/-0.19	2.2+/-0.5	0.06+/0.02-	0.17+/-0.05

*Raw Data, not normalized for body weight

Preliminary examination of the single dose data strongly suggests a significant difference in both the rate and extent of absorption between males and females. Upon closer examination of the weight normalized parameters Cl/F and Vλz/F it appears that these differences are in fact due to body weight. In the comparison of young males to young females, the mean

weight is 61kg for females vs. 82kg for males. This 26% difference is weight, when applied as a correction factor to AUC and Cmax normalized the parameter values such that most of the observed differences disappear. The only difference remaining across the treatment groups are related to the elderly group. In this group, even with dose normalization by weight, statistically significant differences ($p<0.05$) remain. The cause for this is unknown. Given the fact that the increase is also seen for Cmax, as well as AUC, it is possible that whatever pre-systemic clearance takes place with bromfenac is reduced in this population. This could be accounted for by decreased degredation in the stomach due to increased gastric pH, age related reductions in hepatic blood flow, or other metabolic changes brought upon by aging.

Multiple Dose

Multiple Dose Pharmacokinetics of Age and Gender						
	AUC* (mg*h/L)	Cmax* (mg/L)	Tmax (hr.)	T1/2 (hr.)	Cl/F (L/hr/Kg)	Vλz/F (L/Kg)
Young Males	7.8+/-1.7	6.0+/-2.1	0.7+/-0.51	1.6+/-0.8	0.083+/-0.02	0.19+/-0.08
Young Females	9.1+/-2.9	6.1+/-3.2	0.85+/-0.53	1.4+/-0.4	0.103+/-0.038	0.2+/-0.07
Young-Elderly-Males	9.2+/-2.7	6.2+/-2.6	0.63+/-0.21	2.0+/-1.1	0.071+/-0.02	0.2+/-0.1
Young-Elderly-Females	9.8+/-1.9	6.2+/-2.6	1.2+/-1.1	2.4+/-1.1	0.077+/-0.02	0.24+/-0.08
Elderly Males	10.8+/-3.7	6.0+/-1.9	0.63+/-0.14	3.4+/-0.6	0.66+/-0.02	0.32+/-0.11
Elderly Females	13.2+/-3.5	7.4+/-2.3	0.63+/-0.44	2.8+/-0.7	0.064+/-0.015	0.25+/-0.06

*Raw Data, not normalized for body weight

For the most part the differences seen in the multiple dose treatment leg mirror those seen under single dose conditions. Namely that that the very elderly standout as having altered pharmacokinetics when compared to either the young or young elderly. There also appears to be some difference between the young elderly and the young subjects themselves, however, the small number of subjects and the wide range of variability seen makes this conclusion somewhat speculative. Given that the absolute magnitude of the difference is easily matched by the observed variability in the data it does not appear that the differences seen between any of the three groups are significant except for the very elderly.

All in all this study has adequately demonstrated that there are no significant pharmacokinetic differences between men and women following the administration of bromfenac. There does appear to be a age related decrease in bromfenac clearance, however, this difference is small and is easily lost among inter-patient variability except among the very elderly (>75yrs. old). In these subjects bromfenac clearance is reduced, resulting in an almost 2 fold increase in half-life (from 1.6 hrs to 3.4hrs). While in this study there was not a significant degree of drug accumulation, it must be pointed out that in this study the sponsor used a q12hr dosing regimen. Had the sponsor used the q8hr dosing regimen used in the previous dose proportionality study, significant drug accumulation would have occurred for the elderly treatment legs.

Using the formula for accumulation: $R=1/1-e^{-KT}$, one can calculate a range of accumulation factors to fit a variety of dosing regimens and terminal half-lives.

T1/2(K)	T	R
2hrs.(0.3465)	8	1.06
3.4hrs(.2038)	8	1.24
3.4hrs(.2038)	12	1.09

Based on these accumulation factors it appears that, in the very elderly, dosing should be initiated on a q12hrs. regimen, instead of a q8hr regimen.

E. Food Effects

Food/Fasting Study (792-A-118-US)

As was noted in the absolute bioavailability study (#107), food has a significant impact on the bioavailability of the bromfenac dosage form. In order to investigate this issue more thoroughly, the sponsor conducted two additional in vivo biopharmaceutic studies to evaluate the effect of food under varying conditions. This study was designed to evaluate the effect the timing of a high fat meal on the absorption of bromfenac. The study had a total of four treatment legs:

a.) 50mg of bromfenac in a fasted state
b.) 50mg of bromfenac 1.5 hours after a high fat meal
c.) 50mg of bromfenac 2.5 hours after a high fat meal
d.) 50mg of bromfenac 3.5 hours after a high fat meal

Each leg had a 24 hour wash-out period between legs and all dosing occurred following a 10 hour supervised fast. The high fat meal used was the "FDA High Fat Breakfast" from the 1984 controlled release guidelines.

A total of 12 subjects were enrolled in the trial (8men, 4women). All subjects completed the trial, however, the data from one subject (#6) was excluded from the pharmacokinetic data analysis as this subject had plasma levels below the MQC during dosing leg b (1.5 post-prandial). Plasma samples were obtained for 10hrs. post-dosing. Reproduced below is a summary data table extracted from the attached study summary in Appendix I, pages 30-35.

Timing of Meals and Food Effect						
	AUC (mg*h/L)	Cmax (mg/L)	Tmax (hr.)	T1/2 (hr.)	Cl/F (L/hr/Kg)	MRT_{oral} (hr)
Fasted	6.8+/-3.3	3.6+/-1.5	0.82+/-0.5	1.1+/-0.4	0.13+/-0.05	1.9+/-0.5
1.5hr Post Prandial	1.9+/-1.3	1.1+/-0.69	1.4+/-0.98	1.2+/-0.3	0.44+/-0.23	2.4+/-0.7
2.5hr Post Prandial	1.6+/-0.94	0.89+/-0.52	1.3+/-0.76	0.9+/-0.2	0.61+/-0.36	2.1+/-0.4
3.5hr Post Prandial	1.9+/-0.95	1.3+/-0.77	1.2+/-0.52	1.1+/-0.6	0.4+/-0.13	2.1+/-1.0

The results of this trial demonstrated that a high fat meal caused a significant decrease in the extent of absorption of bromfenac for all fed treatment legs. The duration and magnitude of the food effect with bromfenac is remarkable. While the precise mechanism is

unknown it is thought that it must be due to an absolute decrease in bioavailability. The lack of consistent significant differences in MRT_{oral} suggest that the lower plasma levels are not due to a decreased rate of absorption. This is further borne out by a Wagner-Nelson analysis carried out by the sponsor (page 32, Appendix I) that shows that the overall rate of absorption is not significantly different between the treatments. It must, therefore, be due to an absolute decrease in the amount of drug available for absorption. Bromfenac itself is soluble in water, but in the presence of acid cyclizes into AHR-10240 (bromfenac's primary inactive metabolite). While this formation of AHR-10240 undoubtedly is the cause of some reduction in bioavailability, it is not a complete answer as one of the functions of food is to buffer the stomach contents such that even with increased stomach acid output, the pH of the stomach with food is above the normal fasting value of 1.

The net result of this study is to further re-inforce the prohibition of taking this product with or around meal times. The prolonged nature of the food effect on this product is remarkable. Normally the recommendation for controlled release products is to take them at least two hours before or four hours after a meal. With bromfenac it appears that similar advice and labeling should be considered.

Food/Antacid Interaction Study (792-A-108-US)

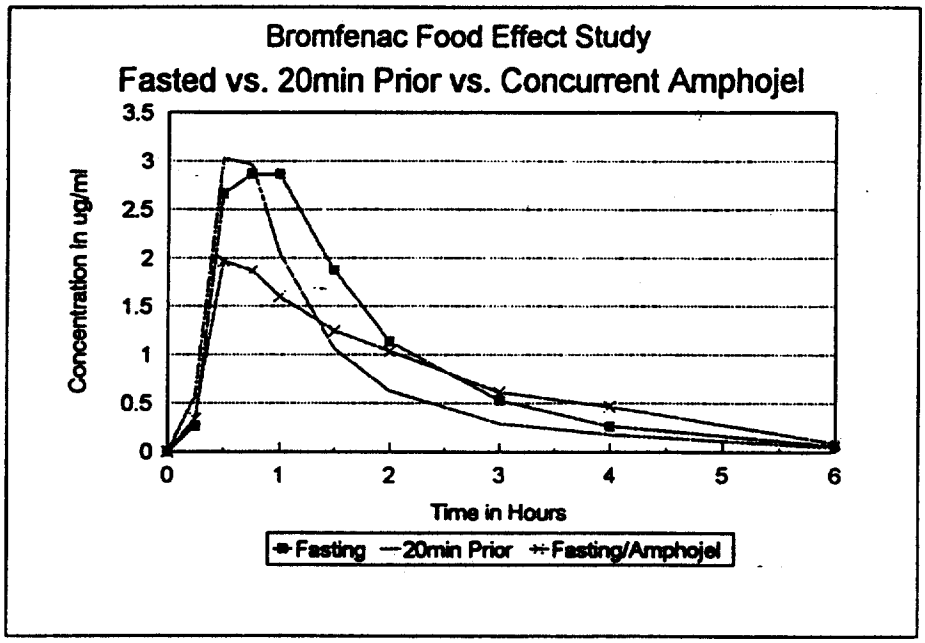
In this study the sponsor was seeking to demonstrate whether or not the administration of antacid in conjunction with dosing would improve the oral bioavailability of bromfenac. The theory being the the antacid would slow or halt the conversion of bromfenac into AHR-10240 (bromfenac's primary metabolite) allowing for an increase in the amount absorbed. In this study twenty healthy male subjects received the following treatments in a random order:

1.) 1x50mg bromfenac capsule, fasted
2.) 1x50mg bromfenac capsule, 20min. before a standard breakfast
3.) 1x50mg bromfenac capsule, immediately following a standard breakfast
4.) 1x50mg bromfenac capsule, 1 hour following a standard breakfast
5.) 1x50mg bromfenac capsule, with 30ml of aluminum hydroxide (Amphojel®)

These treatments were separated by a two-day washout period between all treatments. Reproduced below is a summary data table extracted from the summary study report attached in Appendix I pages 36-40. [*Note: In the summary data table below, treatments 3 and 4 have been excluded as the performance of the bromfenac capsule under these conditions has already been demonstrated. The attached data in Appendix I contains the results for all treatments.*]

Antacid, Timing of Meals and Food Effect					
	AUC (mg*h/L)	Cmax (mg/L)	Tmax (hr.)	T1/2 (hr.)	MRT_{oral} (hr)
Fasted	5.2+/-2.9	3.9+/-1.9	0.9+/-0.6	1.0+/-0.3	1.8+/-0.3
20min. Prior	4.0+/-1.4	3.7+/-1.6	0.6+/-0.2	1.2+/-0.4	1.7+/-0.5
Amphojel®	4.4+/-1.8	2.3+/-1.3	1.3+/-1.3	1.1+/-0.3	2.3+/-0.7

The results of this study are somewhat suprising in that the concurrent administration of antacid did not enhance or accelerate the absorption of bromfenac in the fasted state. Ideally it would be thought that under fasted conditions the antacid would have decreased the rate of bromfenac degredation due to acid cyclization of the amide, thereby making more bromfenac available for absorption. Instead, the antacid lowered both the amount and rate of oral absorption bromfenac in vivo (see figure below).



As for administering the dosage form 20minutes prior to a meal, it is apparent that even though bromfenac is rapidly absorbed, the 20min. interval was too short to allow for complete absorption. As was noted in the previous study, the recommendation that dosing with controlled release products occur 2 hours before or 4 hours after a meal seems to also apply to the immediate release form of bromfenac.

As for the overall effect of food on the bromfenac dosage form, these two studies have confirmed the previous finding in study (#107) that the absorption of bromfenac is strongly influenced by food. The administration of a high fat breakfast severely curtailed drug absorption by lowering the overall extent of absorption by 75% and peak plasma levels by 65%. Concurrent administration with meals, although a common recommendation with most NSAID's cannot be made with this product without running the risk of a therapeutic failure due to poor absorption. The concurrent administration of an antacid with bromfenac causes a statistically significant decrease in the resulting plasma levels in comparison to fasting plasma levels such that its routine use clinically cannot be recommended.

F. Pharmacodynamics of Food/Analgesia (792-A-311-US)

This study was a multi-phase investigation of the pharmacodynamics of bromfenac and meals. The study was divided into three phases:

Phase I- A dose ranging trial of five doses of bromfenac and placebo in the dental pain model under fasting conditions in patients.

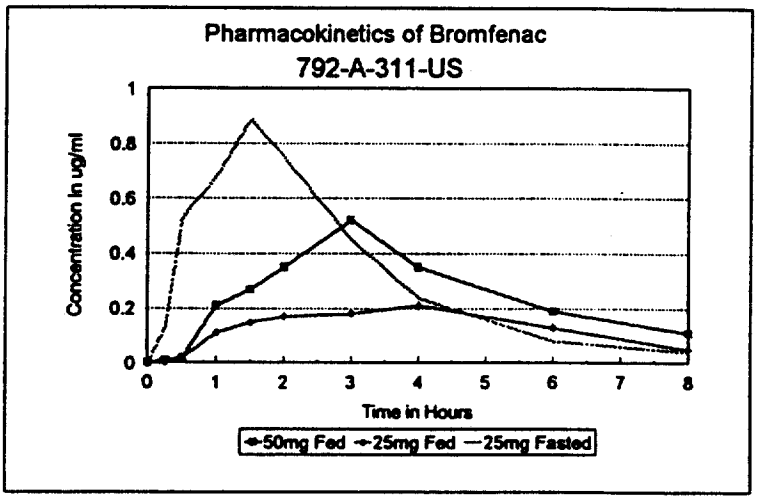
Phase II- A single dose trial to assess the impact of various diets on bromfenac.

PhaseIII- A double blind placebo controlled, randomized parallel, single center, food-controlled, PK/PD analgesia study in patients.

By its very nature this trial was designed to be multi-objective trial with varied endpoints. The primary review of this trial has been done by Dr. John Hyde, FDA Medical Officer. From a pharmacokinetic/pharmacodynamic standpoint the most interesting portion of this trial as it relates to understanding the food effect is Phase III. In this phase of the study the subjects received either placebo or bromfenac as 25mg fasted, 25mg fed, or 50mg fed.

Phase III.

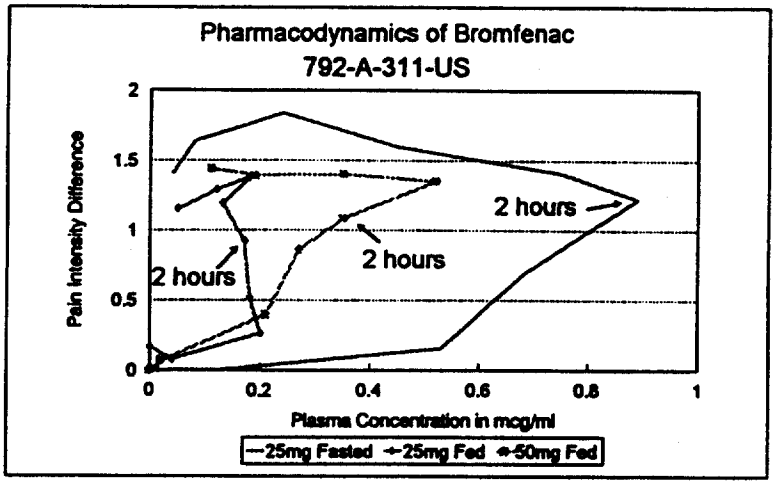
As noted above, in this portion of the study 80 patients were randomized to receive either placebo or bromfenac as 25mg fasted, 25mg with food, or 50mg with food. During the 8 hour assessment interval plasma samples were collected for bromfenac analysis at the following times: prior to dose administration, and at 0.25, 0.5, 1, 1.5, 2, 3, 4,6, and 8 hours after dosing. During the observation interval the subjects were requested to provide feedback on their pain at various timepoints. For the purposes of this review PID data (Pain Intensity Difference) measures will be used as a dynamic endpoint. This value is calculated by taking the absolute change in pain on a 4 point visual analog scale and plotting it out relative to the baseline pain assessment. PID scores of at least 1 are considered evidence of significant pain relief. The results of this phase of the trial are presented below first as a plot of the mean pharmacokinetic data generated in this trial: (see Appendix I, pages 41-52 raw data and additional analysis)



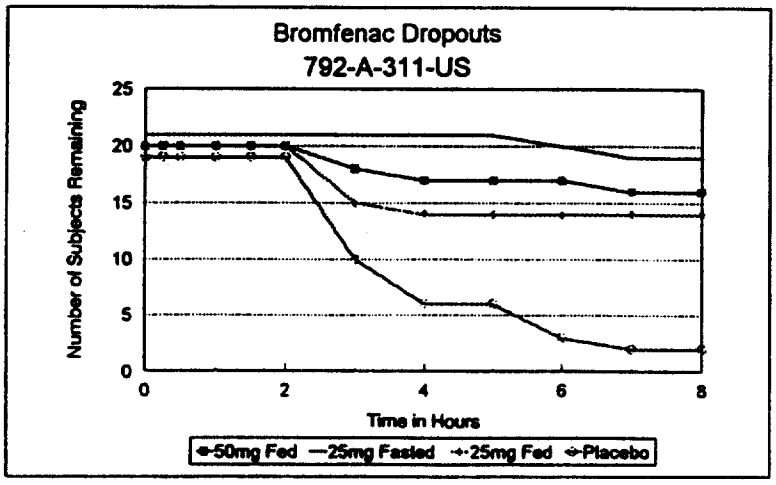
The data from this trial of food effects is very similar to that seen with any of the other food effect trials. Namely that there are large reductions in the bioavailability of bromfenac with the administration of food.

	25mg Fasted	25mg Fed	50mg Fed
AUC(ug*hr/mL)	2.71+/-1.35	1.29+/-0.43	2.34+/-0.92
Cmax(ug/mL)	1.24+/-0.77	0.33+/-0.17	0.70+/-0.38

From a pharmacodynamic standpoint, the data is a little bit different. Reproduced below is a plot of the plasma concentration versus PID for the three treatments. The resulting hysteresis loops have not been collapsed.



The data from this analysis suggests that even with the loss of most of the drug to bioavailability factors, sufficient drug is left to exert a therapeutic effect. For if we define meaningful pain relief as a PID score change of at least 1 unit (on a 4 point scale), then by 2 hours even the fed 25mg dose has achieved this level of pain relief. Furthermore, if one looks at the relationship of the PID scores across the treatments it appears that in reality that the 25mg fed dose has not lagged that badly behind the fasted 25mg dose. Now it is true that this is mean data and the raw hysteresis loops are all over the place and are basically uninterpretable, however, if we look at the dropout rate-a pretty unbiased measure of pain relief, we again see a similar pattern:



The dropout data clearly suggests that even though there is a major reduction in plasma levels, sufficient drug is available to the active site to be effective in an acute pain model. The fact that the 25mg fed dose still separates from the placebo group in term of dropouts, and in fact has a dropout rate comparable to the 50mg fed dose suggests that bromfenac is a very potent

analgesic and that the current 25 and 50mg dosage form contain excess bromfenac to make up for its poor bioavailability. While this is not the preferred way to overcome a problem with bioavailability, it is effective in this case, as the 25mg fed dose clearly has some degree of efficacy.

G. Renal Insufficiency (792-A-101-US)

The use of bromfenac in subjects with renal insufficiency was investigated in two distinct target populations: the moderate to severely impaired (Creatinine Clearance <60ml/min) and in dialysis patients. In this parallel group study each treatment group received a single 50mg dose of bromfenac under fasting conditions. Patients in the dialysis group were dialyzed prior to dosing. In addition to pharmacokinetics on total drug, the sponsor also analyzed both blood and dialysate for unbound bromfenac to see if renal dysfunction altered bromfenac protein binding. A total of 40 subjects were enrolled in this trial (18 normal, 12 impaired, 10 dialysis) and all subjects completed the trial. Both total and free bromfenac parameter values are summarized below, detailed study results are attached in Appendix I as pages 42-48.

Pharmacokinetics in Renal Impairment			
	Normals	Impaired	Dialysis
AUC(ng*h/mL)	6062+/-2830	6866+/-4003	5127+/-2095
AUCu(ng*h/mL)	9.7+/-4.6	10.9+/-6.4	14+/-4.9
Cmax(ng/mL)	3424+/-1409	3898+/-2232	3279+/-1950
Cmaxu(ng/mL)	5.5+/-2.4	6.3+/-3.8	9.0+/-5.4
Cl/F(L/H/KG)	0.13+/-0.05	0.12+/-0.07	0.17+/-0.11
CLu/F (L/H/KG)	79+/-25.4	72.2+/-34.0	58.4+/-33.7
Vss/F (L/KG)	0.149+/-0.067	0.224+/-0.232	0.243+/-0.161
Vss,u/F (L/KG)	90.8+/-36.4	130.4+/-108.9	80.3+/-34.3
Tmax (hr)	0.9+/-0.3	1.8+/-0.9	1.7+/-1.0

The results of this trial suggest that subjects with renal insufficiency show only modest alterations in bromfenac pharmacokinetics. While AUC is increased for these subjects this appears to be due to an increase volume and a corresponding reduction in clearance. While these differences are detectable it should be noted that while the plasma half-life doubled to 1.8 hours in dialysis patients, this places it in the normal range for bromfenac. The abnormal group, in terms of plasma half-life, is the normal volunteer group with a plasma half-life of less than one hour. There is no apparent reason for the observed short half-life in this group.

As for the utility of dialysis as a treatment for overdosage, the dialysis patients in this study underwent a second dosing of bromfenac during a routine dialysis treatment. Venous and arterial blood samples were obtained along with samples of the dialysis fluid itself. Analysis of this data showed minimal differences between venous and arterial levels suggesting that due to the high degree of protein binding of bromfenac (>99%) that dialysis would not be a useful therapy in overdosage situations (see page 49, Appendix I).

Even though this study did not demonstrate any overt need for a dosage reduction in the presence of renal impairment, the use of bromfenac in these patients is cautioned. The

mechanism of action for bromfenac, like all other NSAID's, involves the inhibition of cycloxygenase activity at the site of inflammation and pain. Cycloxygenase is also, however, involved in the regulation of glomerular filtration in the kidney. Blocking the activity of cyclooxygenase has the net effect of lowering glomerular filtration and worsening the subjects renal function. The present study, being a single dose study, is insufficient to assess the magnitude of this effect in vivo. Bromfenac, like all other NSAID's, should be used with caution in subjects with impaired renal function as it may worsen the condition.

H. Hepatic Insufficiency (792-A-103-US)

As noted in the first study reviewed (#102), bromfenac is extensively metabolized with less than 1-2% of a radiolabeled dose being excreted in the urine unchanged. Because of this high degree of metabolism it is desirable to assess the impact of hepatic insufficiency on the pharmacokinetics of bromfenac. Unlike renal insufficiency where there are accepted markers of renal function (creatinine clearance, inulin clearance, etc.) the assessment of hepatic function is problematic and has tended to be based on clinical observation (degree of fluid retention, edema, mental status, etc.). For this study the Child-Turcotte criteria was used to assign subjects to functional groups. This method of scoring uses bilirubin, albumin, nutritional status, and degree of ascites as criteria. A score of 0-4 is normal, 5-7 indicates mild hepatic impairment, 8-12.5 moderate impairment, and greater than 12.5 severe impairment. A total of 33 subjects were enrolled in this trial 17 impaired and 16 normals. The mean Child-Turcotte score in the impaired group was 6+/-2, indicating that the group was composed primarily of mildly impaired subjects.

All subjects in the trial received a single 50mg dose of bromfenac following an overnight supervised fast. Blood was collected for both plasma bromfenac analysis and for protein binding studies. All subjects completed this study, however, the data from subject #9 was removed from the data analysis as he was determined to be a protocol violator (he was too heavy; 143kg vs. upper limit of 100kg for his size). Reproduced below is a summary table of the results extracted from the study summary in Appendix I, pages 61-67.

Pharmacokinetics in Hepatic Impairment		
	Normals	Impaired
AUC(ng*h/mL)	9200+/-4600	14700+/-7200
AUCu(ng*h/mL)	9.5+/-4.44	16.6+/-10.0
Cmax(ng/mL)	5700+/-2500	6100+/-1600
Cmaxu(ng/mL)	5.9+/-2.6	6.6+/-1.6
Cl/F(L/H/KG)	0.1+/-0.05	0.06+/-0.04
CLu/F (L/H/KG)	96+/-57	59+/-35
Vss/F (L/KG)	0.14+/-0.07	0.13+/-0.04
Vss,u/F (L/KG)	138+/-80	120+/-39
T1/2 (hrs)	2.4+/-1.5	3.3+/-1.5
fu(%)	0.10+/-0.01	0.11+/-0.02

Analysis of both the total and free bromfenac suggests that in th presence of hepatic insufficiency the clearance of bromfenac is greatly reduced. In this study with subjects with mild hepatic impairment AUC increased by approximately 60%, while clearance of both total and unbound bromfenac declined by 40%. The degree of protein binding remained constant throughout the study.

As part of the safety work-up from this study the sponsor undertook a step-wise linear regression of various clinical parameters (albumen level, PT, SGOT, SGPT, etc) to identify any routine clinical parameter which is associated with the reduced clearance of bromfenac. The regression was carried out using both raw data and log transformed values. A summary of the results is presented below:

Partial R^2 From Stepwise Regression				
	CL/F	AUC	Clu/F	AUCu
Untransformed	0.38(bilirubin)	0.49(PT)	0.50(PT)	0.71(PT)
	0.15(alk phos)	0.22(CrCl)		0.10(CrCl)
Transformed	0.52(bilirubin)	0.43(bilirubin)	0.67(PT)	0.67(PT)
	0.08(alk phos)	0.23(height)	0.08(bilirubin)	0.06(CrCl)
	0.07(age)			

From this analysis the sponsor has developed a regression line for AUCu for the two significant parameters, bilirubin and prothrombin time (PT). These regressions are attached as page 56 in Appendix I. As a reviewer, I am not convinced by their analysis of these factors. I am troubled by the sponsors conclusion that PT is a reliable indicator of hepatic status and their conclusion that subjects with PT's greater than 13.5 seconds should have their doses reduced. While I am in favor of reducing the dose in hepatically impaired subjects, PT is not a reliable parameter value as there is no standard normal range. In a clinical laboratory PT for a patient is determined versus a daily control value that each lab has to establish daily. I am uncomfortable with a non-standardized test being used in this way.

As for bilirubin, the partial R^2 that the sponsor cites as demonstrating a correlation between AUCu and bilirubin (0.59) is not in their study report. While it is true that a bilirubin of 1.3 is indicative of hepatic insufficiency, I am again uncomfortable in recommending its adoption as a standard. At the present time the label should merely indicate that in cases of suspected or demonstrated hepatic insufficiency, therapy with bromfenac should be initiated with q 12hr dosing initially.

I. Bioequivalency

During the clinical development of this product the sponsor used product produced in Montreal, Canada. Anticipating large scale manufacture the sponsor is planning on moving production to Guayama, Puerto Rico. In order to validate that the clinically studied "Montreal" product is identical to the newly formulated product the sponsor undertook a four-way crossover study to evaluate the bioequivalency of the 25 and 100mg capsule products produced at the two sites.

This study was designed to provide 24 complete sets of data to establish bioequivalency. A total of 44 subjects were enrolled and 20 subjects were removed from the trial. Subjects #1-15 were removed from the study as they accidentally received the same treatment for periods 1, 2, and 3. They were replace by subjects #101-115. Subject #110 was removed from the data analysis as an outlier test comparing studentized residuals identified an unusually large residual for the log transformed Cmax of the 100mg formulation. The remaining subjects data was not included in the final analysis as the sponsor, after removing the first 15 subjects, oversubscribed the trial in an effort to get 24 completers. Reproduced below is a summary data table extracted from the study summary report in Appendix I, pages 68-74.

Bioequivalency:Clinical vs. To-be-marketed			
25mg	AUC(mg*h/L)	Cmax (mg/L)	Tmax(h)
Montreal(ref)	3.04+/-1.0	1.9+/-0.7	1.25+/-0.75
(test)	3.19+/-1.06	2.2+/-0.9	1.24+/-0.64
90% Confidence Intervals*	97-112	97-123	83-127
100mg	AUC(mg*h/L)	Cmax (mg/L)	Tmax(h)
Montreal(ref)	15.14+/-4.01	9.4+/-3.3	1.28+/-0.89
(test)	14.93+/-4.29	10.0+/-3.7	1.25+/-1.02
90% Confidence Intervals*	89-107	92-120	68-127

*Based on log transformed data

All in all the results from this study indicate that the to-be-marketed product is bioequivalent to the clinically studied product. The study itself was not the best run study, but in the end the sponsor ended up with enough evaluable subjects to complete the analysis. The sponsor should, however, revise their study procedures to prevent the occurrence where the same treatment was packaged for three different treatment legs.

J. Drug Interactions

As part of the development of this product the sponsor undertook a number of in vivo drug-drug interaction trials. A total of six trials were done with methotrexate, warfarin, cimetidine, phenytoin, glyburide, and digoxin. The trials themselves are well designed and incorporate, wherever possible, sufficient treatment legs to assess not only the interaction of bromfenac on these drugs, but the effects of these drugs on bromfenac. By using a so-called "two-way" interaction trial format, the sponsor has greatly increased their knowledge base for this drug. The trials themselves have been classified as supportive trials as they do not directly impact on the approvability of bromfenac itself. As supportive trials the results from the trials will be presented in this review in summary format only.

Methotrexate (792-A-113-US)

As a commonly prescribed drug in the treatment of rheumatoid arthritis the interaction between methotrexate and bromfenac was studied in 9 subjects (4males/5females) who were already stabilized on maintenance methotrexate (5-15mg q weekly). Baseline methotrexate

levels were obtained on day 1. Four days prior to the next weekly dose of methotrexate 50mg of bromfenac q 8 hrs was initiated. On days 7 and 8 plasma was sampled for bromfenac. On day 8 plasma was also collected for methotrexate. The detailed results of this trial are attached in Appendix I as pages 75-84.

The results of this trial are open to interpretation, while the observed differences in the pharmacokinetic parameters are small, they are on the basis of confidence interval testing statistically significant for every comparison between bromfenac, methotrexate, and 7-OH methotrexate. This finding, however, has to be balanced with the fact that the study had only nine subjects in it and it lack adequate statistical powering. If one examines the plasma level time curves for bromfenac and methotrexate it does not appear that a drug-drug interaction of any significant magnitude took place. As for the 7-OH metabolite of methotrexate, it's clearance did decrease by 16% and its AUC increased by ~30%, however, 7-OH methotrexate is a variable compound and the test is without statistical power.

The results of this study indicate that the clearance of the 7-OH metabolite of methotrexate may be reduced. The clinical significance of this reduction and resultant elevated levels will be referred to the reviewing medical officer for consideration.

Warfarin® (792-A-112-US)

Warfarin® (coumadin) is a drug used to prolong the bleeding time by inhibition of vitamin K synthesis in the gastrointestinal tract. It is also a highly protein bound drug that has been the a source of classical protein binding displacement studies since the realization in the late 1950's that aspirin and phenylbutazone caused displacement of coumadin from binding sites. In this open-label study 15 healthy adult males received sufficient coumadin to maintain prolonged bleeding times(PT) in the range of 1.25 to 1.5 times baseline (not to exceed 20seconds). The mean dose of coumadin was 6.8+/-1.9mg/day Once the subjects were stable on their regimen each subject would receive 50mg of bromfenac every 8 hours for 10 days at which time plasma was drawn for both the assessment of bromfenac and coumadin. Following this treatment phase the coumadin was withdrawn and after a return of PT to baseline values, the subjects received a second 3 day course of bromfenac alone to provide comparative kinetic values. The detailed results of this trial are attached in Appendix I as pages 85-96.

In general there were only small significant difference in the pharmacokinetics of either bromfenac or coumadin when administered concomitantly. Bromfenac plasma levels (Cmax and AUC) were increased and clearance was decreased by about 16% for both total and free bromfenac. Coumadin pharmacokinetics were essentially unchanged for either the R-, or S-enantiomers and the fraction unbound for racemic coumadin was unchanged. There was no significant effect on PT times when bromfenac was added to coumadin.

Cimetidine (792-A-110-US)

Cimetidine is a common drug to test for interactions with as it is capable of interacting at the level of the metabolizing enzyme (CYP3A). At the present time the sponsor has not done specific iso-enzyme testing with bromfenac to determine whether or not it would interact with cimetidine via this mechanism. In lieu of such in vitro work the sponsor conducted an open label study in 24 adult males. Each subject received either 50mg of bromfenac q 8 hours for 4 days, followed by an additional 4 days of bromfenac with 400mg of cimetidine q 12 hours, followed by 4 days of 400mg cimetidine q 12 hours alone or the same treatment in reverse order.

In doing so the sponsor was able to investigate both the effect of adding bromfenac to cimetidine and the effect of adding cimetidine to bromfenac. The detailed results from this study are attached in Appendix I as pages 97-105.

No significant differences were noted in the pharmacokinetics of cimetidine when bromfenac was co-administered. Bromfenac pharmacokinetics were markedly changed. Co-administration of cimetidine and bromfenac resulted in about a 59% increase in Cmax, a 20% increase in AUC, and a 20% decrease in Cl/F for bromfenac. Examination of the plasma level time curve for bromfenac (page 88, Appendix I) suggests that the mechanism is not metabolic (T1/2 is unchanged) but is due to the suppression of gastric acid allowing for a higher fraction of the total dose of bromfenac to be absorbed. The suppression of gastric acid is postulated to enhance absorption by diminishing the conversion of bromfenac to its cyclic amide metabolite (AHR-10240). A similar attempt at suppression of gastric secretions was attempted with Amphojel® in study #108, however, in that study the results were less than expected, possibly due to inefficient buffering of the stomach contents. Because of the marked increase in peak plasma levels, concomitant administration of bromfenac with cimetidine should be initiated with low doses and titrated to effect.

Phenytoin (792-A-114-US)

Phenytoin is a unique drug in that it is considered both a narrow therapeutic index drug and an inducer of hepatic microzomal enzymes (CPY3A4). In addition to its narrow therapeutic index, phenytoin is highly protein bound and has the potential to interact with other highly protein bound drugs. Furthermore, phenytoin's metabolism is capacity limited, i.e., the metabolic processes responsible for the elimination of phenytoin can be saturated, resulting in rapid and unexpected increases in plasma concentrations in a non dose proportional manner. At such a time phenytoin is said to be undergoing "non-linear" pharmacokinetics of the Michaelis-Menton type.

This study was done to assess whether or not bromfenac had a significant impact on either the protein binding or metabolism of phenytoin. The study was designed with three phases. Phase I involved the administration of 50mg of bromfenac to 12 healthy male subjects q 8 hr for 7 days to determine the baseline pharmacokinetics of bromfenac. Following this in Phase II each subject received a dose of 300mg of phenytoin daily (target blood level between 7 and 14ug/ml) for one week. In Phase III bromfenac would be introduced on a q 8 hr schedule for 7 days. The results from this study are attached in Appendix I as pages 106-112.

In regard to the interaction between phenytoin and bromfenac, the pharmacokinetics of phenytoin are essentially unchanged with only a 9% decrease in Cmax and an 11% decline in AUCss. Bioequivalence testing using the two 1-sided test procedure did not detect any significant difference for either Cmax or AUCss for phenytoin. As for the degree of binding, the unbound fraction of phenytoin was essentially unchanged. There was increase in the AUCu of phenytoin from 29.7 to 34.4 (mg*hr/L) but as each value for AUCu is associated with a 30+% C.V. this change is not considered significant.

As for bromfenac, its pharmacokinetics are greatly altered by the co-administration of phenytoin. Both AUC and Cmax for bromfenac were 40% lower compared to baseline, while Cl/F was almost doubled. There was no change in either T1/2 or Tmax. Possible explanations of this increased clearance of drug include alterations in plasma protein binding or metabolic induction. As the free fraction of bromfenac was unchanged in this study it seem most likely that

the reduction in circulating bromfenac levels is due to metabolic induction of CPY3A4 by phenytoin. While speculative, this finding of metabolic induction gives at least a preliminary identification of the metabolizing enzymes responsible for the elimination of bromfenac. While the concurrent administration of bromfenac does not call for dosage adjustment for phenytion, the clinician should be aware of the potential loss of efficacy for bromfenac secondary to induced metabolism.

Glyburide (792-A-109-US)

Glyburide is a so-called second generation sulfonylurea used in the treatment of Type II diabetes. Unlike the other drug interaction studies reviewed up to this point, because of the anti-diabetic effect of glyburide, this study could not be done in normal volunteers. Nor could the effect of glyburide on bromfenac be determined in these patients as they could not stop their glyburide to accommodate the two-way interaction design. The study was designed as a double-blind, placebo controlled, two-way crossover study in 12 diabetic subjects. The study itself while adequately designed had to be repeated. According to documents provided by the sponsor the blood samples were ***stolen*** from the clinical laboratory prior to analysis and the trial had to be repeated. During the repeat phase of the trial one subject dropped out due to a fever. Attached in Appendix I as pages 113-117 are the results from this trial along with the study summary sheet for the trial.

Although it was not possible to do a strict two-way look at the interaction between bromfenac and glyburide, there does not appear to be a difference in the pharmacokinetic profile of either. The two glyburide treatments, with and without bromfenac, easily pass the bioequivalency test (90% confidence intervals) and the effect on glucose regulation by glyburide is indistinguishable under either regimen. As for bromfenac, comparison of the results from this study with other studies does not reveal any marked differences in bromfenac pharmacokinetics.

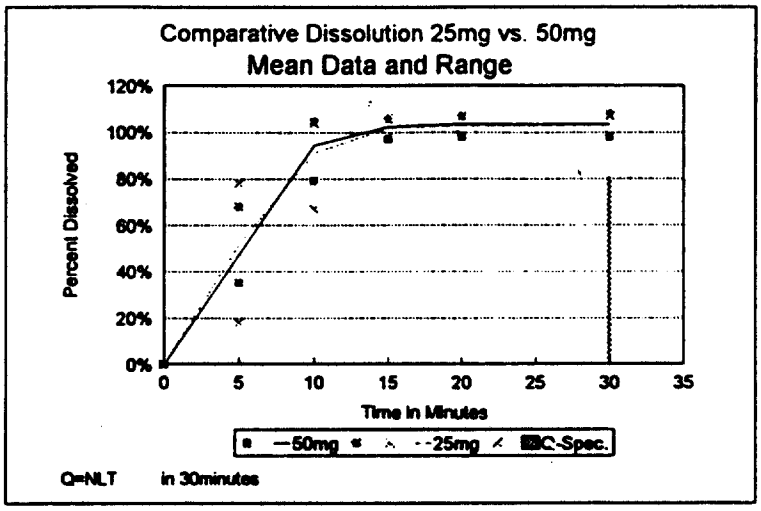
Digoxin (792-A-116)

Digoxin is a frequently administered medication used to treat cardiac arrhythmias including atrial flutter and fibrillation among other things. It has a narrow therapeutic range of 0.5 to 2 ng/ml. Because of its inotropic effects drug-drug interaction studies cannot be performed in healthy volunteers, but must be done in patients. In this study 12 subjects (6M/6F) who had been receiving digoxin doses between 0.18mg and 0.5mg a day for at least 1 month were enrolled in the trial. On study days 1 and 8, serial blood and urine samples were collected to study the pharmacokinetics of digoxin. Bromfenac pharmacokinetics were studied on day 8. From day 2 to 7, brmofenac 50mg was administered every 8 hours. Attached as pages 118-122 are the detailed trial results and accompanying study summary sheet.

Analysis of plasma digoxin concentrations before and after bromfenac administration revealed a small increase in peak digoxin concentrations (1.71+/-0.8ng/ml vs 2.04+/-0.88ng/ml) and AUC24hr (17.88+/-8.5 vs. 21.38+/-10.82). Analysis of electrocardiogram data (QT interval, QRS interval, and PR interval) showed no change in values across the treatments which would be associated with digoxin. In light of the lack of a significant dynamic effect, these changes in Cmax and AUC are not considered significant.

K. Dissolution

One of the reasons bromfenac was developed as an analgesic rather than as an anti-inflammatory agent was its rapid absorption profile, relative to other NSAID's. This rapid absorption profile is more than matched by the products in vitro dissolution performance. Contained in the original NDA was summary in vitro dissolution data on lots of drug that were used in the clinical development of bromfenac (Appendix I, pages 123-124). This data along with the sponsor's proposed in vitro dissolution specification is presented graphically in the following figure.



The specification that the sponsor is proposing is unacceptable as an in vitro dissolution procedure. It would allow for lots to have a wide range of possible dissolution profiles and would be unlikely to ever fail a lot.

Since the time of the original NDA submission this issue has been taken up on by Dr. Bart Ho, review chemist, FDA. In negotiation with the company, Dr. Ho has obtained the sponsors agreement to a new in vitro dissolution specification for bromfenac. The revised specification and method are as follows:

Apparatus:
Speed:
Media:
Volume:
Time:
Q:

According to Dr. Ho, "...this new specification is well within the range of manufacturing variability that the sponsor has seen in their internal dissolution studies and should not present a problem for them." While somewhat uncomfortable with the non-standard time, i.e, 20 minutes, as the sponsor has already agreed with this method and specification I see no need to alter it as it seems to correlate better with the observed rapid absorption profile of bromfenac.

V. Conclusions

After reviewing the material presented by the sponsor in this NDA the following conclusions can be made:

1. Bromfenac is rapidly and incompletely absorbed with an absolute bioavailability of only 67%.
2. The reason for the low oral bioavailability seems to be related to the action of stomach acid on bromfenac causing the formation of a primary degerdant/metabolite.
3. Bromfenac plasma levels peak at about 1-1.5hrs after dosing.
4. Bromfenac has a short plasma half-life in normal subjects ranging from 0.9-2.4 hours. The best overall estimate of half-life is ~1.5hrs.
5. Bromfenac is dose proportional over a range of doses from 5 to 100mg.
6. Bromfenac is excreted in the urine as a cyclic amide metabolite with very little unchanged bromfenac or bromfenac conjugates present.
7. In vivo biopharmaceutic studies have shown that there are no significant differences between males and females or the young and young elderly. Subjects older than 75 yrs old do have a lower clearance and a prolonged plasma half-life.
8. Bromfenac's bioavailability is severely affected by food. Multiple studies by the sponsor have shown that even up to 3.5 hours after a high-fat meal, both peak plasma levels and AUC are depressed by up to 80%. This reduction in bioavailability is thought to be due to the local effects of stomach acid upon bromfenac
9. Even with the massive food effect, in an acute pain model, fed doses of 25mg of bromfenac were able to demonstrate some degree of efficacy. In the same study fed 50mg doses of bromfenac were almost indistinguishable from fasted 25mg doses in terms of dropout rates and PID score.
10. Concomitant administration of antacid does enhance the bioavailability of bromfenac, however, when combined with cimetidine the bioavailability of bromfenac is greatly increased.
11. There are no drug interactions between bromfenac and digoxin, coumadin, glyburide, or methotrexate. Phenytoin appears to induce the metabolism of bromfenac, causing a 40% decrease in both peak plasma levels and AUC.
12. In mild to moderate renal failure and in dialysis patients, the pharmacokinetics of bromfenac were essentially unchanged.
13. In mild hepatic failure, the clearance of bromfenac was markedly reduced. In these patients bromfenac should be administered using the lowest dose and the longest feasible dosing interval.
14. The sponsor has proposed a dissolution specification of NLT at 20minutes. This specification was worked out between the FDA chemist and the sponsor.
15. Once acceptable labeling can be developed the product will be approvable from a biopharmaceutic perspective.

VI Comments

1.) At the present time the sponsor is proposing to label bromfenac for either q6 or q8hour dosing in acute analgesia. None of their pharmacokinetic trial utilized a

VI Comments

1.) At the present time the sponsor is proposing to label bromfenac for either q6 or q8hour dosing in acute analgesia. None of their pharmacokinetic trials utilized a q6hr dosing strategy. All of the multiple dosing that took place as part of the pharmacokinetics work-up of bromfenac did so as either q8 or q12hr. Having recognized this oversight on the sponsor's part, I do not think that it will have a significant effect on the disposition of bromfenac. Using a half-life of 2.4 hours the accumulation index one would expect for bromfenac upon q6hr dosing would be 1.21. While this does indicate that bromfenac would accumulate, it does not appear excessive and seems to fit into the observed range of variance in parameter estimates for AUC and Cmax.

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Senior Pharmacokineticist
Div. of Pharmaceutical Evaluation-III

Peer Reviewer: John Lazor, Pharm.D. 5/2/96

NDA 20-535 (ORIG),
HFD-550/CSO/Koerner
HFD-550(Bashaw)
HFD-880(Fleischer)
HFD-870(Mei-Ling Chen)
HFD-870 (Clarence Bott, Drug, Chron Files)
HFD-860(Malinowski)
HFD-344(Viswanathan)
HFD-205.

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			Pharmacokinetics and Bioavailability				
792-A-102-US GMR 22213 (Leese)	Open-label, single-dose, ^{14}C-labeled metabolic disposition in healthy volunteers	Bromfenac: 50 mg single dose	6 (6M) [6W]	^{14}C-brom: P3152-81 W-AR. Princeton, NJ August 1991	14 Nov 91	The absorption of bromfenac was rapid. The whole blood/plasma ratios of radioactivity averaged 0.2 and remained relatively constant over time. Unchanged bromfenac was the major component found in plasma although not found in urine. Total radioactivity recovered over 4 days from 4 of the 6 subjects averaged 82.4% and 13.2% of the dose in the urine and feces, respectively.	none.

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			Pharmacokinetics and Bioavailability (continued)				
792-A-105-US GMR 22078 (Keane)	Open-label, 4-period crossover, dose proportionality of single and multiple doses in healthy volunteers	Bromfenac: 5 mg, q 8 hr, 25 mg, q 8 hr, 50 mg q 8 hr, 100 mg, q 8 hr for 10 doses	24 (24M) [5B,1NA, 18W]	Bromfenac 25 mg capsules Batch OVTE W-AR Rouses Point NY February 1991 5 mg capsules Batch ITKA W-AR Rouses Point NY July 1991	8 July 91	Pharmacokinetics exhibit linear dose proportionality after single- and multiple-dose administration (q 8 hr) in this dose range. The pharmacokinetics of unbound bromfenac exhibit linear dose proportionality after multiple-dose administration between 25 and 100 mg.	[14 Oct 1991] FDA reviewer's comments on dose timing, collection of urine samples, identification of metabolites, and use of statistical tests were incorporated into the protocol.

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Pharmacokinetics and Bioavailability (continued)							
792-A-107-US GMR 24545 (Swan)	Open-label, randomized, crossover, incomplete block, 4-treatment, 3-period, absolute bioavailability in fed and fasted healthy volunteers	Bromfenac: single dose 50 mg IV bolus over 5 minutes, fasting 50 mg IV bolus over 5 minutes, fed 50 mg oral, fasting 50 mg oral, fed	24 12 IV, fasted; 12 IV, fed; 24 po, fed & fasted (23M, 1F) [23W,1H]	Bromfenac 50 mg capsules Batch OVTF W-AR Rouses Point NY February 1991 Na citrate diluent 10mL amp Batch 2TJV W-AR Rouses Point NY September 1992 Bromfenac lyophilized for injection Batch 2THD W-AR Rouses Point NY September 1992	15 Oct 93	The absolute bioavailability of bromfenac was 67% +/- 20% in fasting subjects. Compared to fasted subjects, the mean AUC decreased by 73% when bromfenac was given orally to fed subjects. Compared to fasted subjects, the mean AUC decreased by 28% when bromfenac was given IV to fed subjects. Thus, the reduction in postprandial bioavailability is largely presystemic with only a minor systemic component.	[20 Sep 1993] Teleconference between sponsor and FDA reviewer. Reviewer questioned conducting study in fed conditions and the pooling of fed and fasted data. Sponsor responded that differences in bioavailability under fed and fasted conditions have been observed; the study was designed to evaluate the mechanism of the food interaction. Sponsor also respc.:ded that the study design offered a balance between observing the fed vs. fasted effects versus exposing subjects to repeated injections.

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Pharmacokinetics and Bioavailability (continued)							
792-A-117-US GMR 24726 (Stoltz)	Open-label, randomized, 3-period crossover, bioavailability of bromfenac formulations used in clinical trials and to be used in marketing, in healthy volunteers	Bromfenac: single dose (clinical trial) 50 mg (clinical trial) 50 mg (marketing) 50 mg	24 (14M, 10F) [2B,21W, 1 oth]	50 mg capsules Batch 0VTF W-AR Rouses Point NY February 1991 50 mg capsules Batch 1VDE W-AR Rouses Point NY April 1992 50 mg capsules Batch A93D046 AWPI Guayama Puerto Rico July 1993	29 Nov 93	Batch 1VDE is bioequivalent to Batch A93D046 when C_{max}, AUC_T, and AUC are considered. The marketing formulation (Batch A93D046) has a slightly higher mean C_{max} and AUC than the clinical formulation batch (0VTF). However, Batch 0VTF is bioequivalent to Batch A93D046 if modest adjustment is made for potency difference.	none.

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Pharmacokinetics and Bioavailability (continued)							
792-A-119-US GMR 24725 (Leese)	Open-label, single-dose randomized, 4-period crossover, comparative bioavailability of capsules used in clinical trials and capsules to be marketed, in healthy volunteers.	Bromfenac: single dose (clinical trial) 25 mg 100 mg (marketing) 25 mg 100 mg	23 (20M, 3F) [1H, 4B, 18W]	Bromfenac 25 mg capsule Batch 1TWG Rouses Point NY December 1991 100 mg capsule Batch 1VDF W-AR Rouses Point NY April 1992 25 mg capsules Batch A93D052 100 mg capsules Batch A93D050 AWPI Guayama Puerto Rico August 1993	27 Jan 94	The clinical trial bromfenac formulation was bioequivalent to the proposed market formulation for both 25 mg and 100 mg strengths when C_{max}, AUC_T, and AUC are considered.	none.

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Pharmacokinetics and Bioavailability (continued)							
AHR-04-US AHR-86-0438 (deDennis)	Open-label, single-dose, 4-period crossover determination of dose proportionality in healthy volunteers	Bromfenac: single dose 25 mg 50 mg 100 mg 200 mg (as solution)	12 (12M) [12W]	oral solution of 10 mg/mL formulation 10282B-32-11-099 (lot numbers 3480A, 3480B, 3480C, 3480D) AH Robins Richmond VA April 1985	25 Mar 85	Bromfenac was rapidly absorbed and eliminated. The degree of plasma protein binding was >99% and independent of drug concentration. The pharmacokinetics of bromfenac were dose proportional over the dose range of 25 to 100 mg for both total and unbound bromfenac.	none.

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				Pilot and Background Studies			
AHR-01-US AHR-85-0310 (Rollins)	Double-blind, single-dose, placebo-controlled, safety and tolerance in healthy volunteers	Bromfenac:[a] single dose 1 mg 5 mg 10 mg 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 50 mg, with meal 50 mg, 30' before meal 50 mg, 60' before meal placebo	28 (28M) [28W]	Bromfenac Batch: 3296 (1 mg capsules) 3297 (5 mg capsules) 3298 (10 mg capsules) 3299 (25 mg capsules) 3300 (50 mg capsules) Placebo: Batch 3301 AH Robins Richmond VA July 1984	2 July 84	Single oral doses as high as 200 mg were well tolerated. Peak plasma concentrations were obtained in 1 hour, $t_{1/2}$ was 1 hour. Little unchanged drug was recovered in the urine. Administration of bromfenac with food decreased the bioavailability of bromfenac.	none.

a: PK only on 10, 50, 150, 50 mg with meal, 50 mg 30' before meal, 50 mg 60' before meal.

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Pilot and Background Studies (continued)							
AHR-03-US AHR-86-0535 (Rollins)	Double-blind, randomized, placebo-controlled, safety and tolerance in healthy volunteers	Bromfenac: 10 mg q.i.d. 25 mg q.i.d. 14 days 50 mg q.i.d. 100 mg q.i.d. 28 days Placebo	24 (6/group) (24M) [24W]	Bromfenac Batch: 3298 (10 mg capsules) 3299 (25 mg capsules) 3300 (50 mg capsules) Placebo: Batch 3301 AH Robins Richmond VA July 1984	13 Mar 85	All dose levels were well tolerated. Based on the multiple trough measurements of bromfenac concentration, there was no evidence of accumulation during multiple dosing.	none.

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Pharmacokinetics in Special Populations							
792-A-101-US GMR 22077 (Rudnick)	Open-label, single-dose, parallel pharmacokinetics in healthy subjects and subjects with impaired renal function	Bromfenac: single dose 50 mg Dialysis patients received 2nd dose 0.5hr before dialysis	18 healthy (14M, 4F) [3B, 1H, 14W] 12 renal impaired (9M, 3F) [5B,7W] 10 dialysis-dependent (7M, 3F) [9B, 1W]	50 mg capsules Batch AHR 4023 AH Robins Richmond VA July 1989	21 Jan 91	Few significant changes in disposition of bromfenac were noted in subjects with varying degrees of renal function. There was a statistically significant but clinically unimportant increase in $t_{1/2}$ of 1 hour when comparing healthy volunteers to patients with either moderately or severely impaired renal function. There was a significant increase in f_u for dialysis subjects. There were no significant differences in CL/F or V/F for unbound bromfenac between subject groups.	none.

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Pharmacokinetics in Special Populations (continued)							
792-A-103-US GMR 22214 (Harris)	Open-label, single-dose pharmacokinetics in subjects with chronic stable liver disease and in healthy volunteers	Bromfenac: single dose 50 mg	32 total 16 healthy (12M, 4F) [5W,11H] 16 impaired (12M,4F) [5W, 3B, 8H]	50 mg capsules: Batch AHR4023 AH Robins Richmond VA July 1989	7 Jan 91	The clearance of bromfenac was altered in the impaired subjects. The $t_{1/2}$ was prolonged and the AUC values for total and unbound bromfenac were higher in the impaired subjects relative to healthy subjects. However, there was a large intersubject variability in the degree of hepatic impairment and CL/F values overlapped considerably between the 2 groups. Differences were most marked in those subjects with the most severe hepatic impairment (those with prolonged PT and elevated serum bilirubin values). Therefore, a dosage adjustment of 1/3 to 1/2 of that of healthy volunteers may be advisable in some subjects, especially those with PT values > 13.5 seconds.	none.

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			Pharmacokinetics in Special Populations (continued)				
792-A-104-US GMR 22220 (Wicht)	Open-label, non-randomized, parallel, effects of age and gender on pharmacokinetics in 6 groups of healthy volunteers: young men,[a] young women, young-elderly men, young-elderly women, elderly men, elderly women	Bromfenac: 50 mg single dose followed by 50 mg q12 hrs for 6 additional doses	44 total 20 young (10M, 10F) [18W, 1H, 1A] 12 young-elderly (6M, 6F) [12W] 12 elderly (6M,6F) [12W]	Bromfenac 50 mg capsules: Batch AHR4023 AH Robins Richmond VA July 1989	8 Jan 91	No differences were noted between men and women for any PK parameter. Differences in PK parameters due to age were noted following both single and multiple doses. The differences due to age were not significant enough to require dosage adjustment for short term use in elderly subjects.	none.

a: young = 18-45 years; young-elderly = 65-74 years; elderly = >/= 75 years

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			Pharmacokinetics in Special Populations (continued)				
AHR-11-US AHR-88-0286 (deDennis)	Open-label, single-dose, PK and protein binding in elderly subjects (age 65-84 years)	Bromfenac: single dose 50 mg	20 (10M, 10F) [20W]	50 mg capsules Batch 3487 AH Robins Richmond VA March 1985	4 Dec 86	Absorption was rapid (t_{max} ≈1 hour) for men and women. The C_{max} and AUC values were higher for women than men. There was no apparent gender effect on clearance and $t_{½}$. When PK results were retrospectively compared for elderly men and young men (from study AHR-04-US), mean AUC values were 24% larger and $t_{½}$ was slightly longer in elderly men. Bromfenac was > 99% protein bound.	none.

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				Drug Interaction Studies			
792-A-109-US GMR 24189 (Harris)	Double-blind, randomized, 2-period crossover, placebo-controlled evaluation of bromfenac and glyburide in diabetic subjects	Glyburide: 10 mg/day AND Bromfenac: 50 mg t.i.d. for 3 days Glyburide: 10 mg/day AND Placebo for 3 days	11 (10M, 1F) [1B,10H]	**Bromfenac:** 50 mg capsules Batch 1TBK W-AR Rouses Point NY March 1991 **Bromfenac placebo** Batch 2TCV W-AR Rouses Point, NY April 1992 **Micronase® 5mg** tablets Upjohn market product NDC 0009-0171-03 DOM unknown SOM unknown	16 Nov 92	Bromfenac pharmacokinetic parameters in these subjects were different when compared to studies in healthy volunteers: concentrations were decreased, t_{max} was increased, V/F was increased, and Cl/F was 2/3 of the lower end of the range. It is possible that gastric stasis in these diabetic subjects and the administration of bromfenac 2 hours after a meal contributed to these results. No significant changes were observed in glyburide pharmacokinetics when bromfenac was administered concurrently. No change was observed in either glucose concentrations or insulin concentrations when bromfenac was administered concomitantly with glyburide.	none.

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TABLE F.2
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			Drug Interaction Studies (continued)				
792-A-110-US GMR 21864 (Fruncillo)	Open-label, randomized, multiple-dose, pharmacokinetic evaluation of bromfenac and cimetidine in healthy volunteers	50 mg bromfenac q8hr or 400 mg cimetidine q12hr for days 1-4; 50 mg bromfenac q8hr and 400 mg cimetidine q12 hr for days 5-8; 50 mg bromfenac q8hr or 400 mg cimetidine q12hr for days 9-12.	24 (24M) [3B,21W]	**Bromfenac** 50 mg capsules: Batch OVTF W-AR, Rouses Point NY February 1991 **Tagamet®**, 400 mg tablets SKF market product NDC 00108-5026-18 DOM unknown SOM unknown	18 June91	Coadministration of cimetidine and bromfenac resulted in a 59% increase in C_{max}, a 20% increase in AUC, and a 20% decrease in the Cl/F of bromfenac. The changes may be due to decreased degradation of bromfenac by gastric secretions that are inhibited by cimetidine. Cimetidine pharmacokinetics were unaffected by coadministration with bromfenac.	none.

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Drug Interaction Studies (continued)							
792-A-112-US GMR 23253 (Leese)	Open-label, nonrandomized, multiple-dose, PK/PD evaluation of bromfenac and warfarin in healthy volunteers	Part 1: Bromfenac 50 mg q8 hr for 3 days Part 2: Warfarin (in dose to prolong PT 1.25-1.5x) for a minimum of 10 days Part 3: Warfarin (in above dose) AND Bromfenac 50 mg q8 hr for 10 days	15 (15M) [5B,10W]	**Bromfenac:** 50 mg capsules Batch 1TBK W-AR Rouses Point NY March 1991 **Coumadin®** 5 mg tablets DuPont Market Product NDC 0056-0169-70 DOM unknown SOM unknown **Coumadin®** 2.5 mg tablets DuPont Market Product NDC 0056-0176-70 DOM unknown SOM unknown	20 Jan 92	Small, statistically significant changes were observed in steady-state PK of both drugs. Bromfenac plasma levels were increased and clearance was decreased by about 16% both for total and unbound bromfenac. Racemic warfarin and its R-enantiomer had slightly higher plasma levels and reduced clearance when given with bromfenac; the S-enantiomer showed opposite changes. These differences were not reflected in any clinically relevant changes in either PT or platelet aggregation. Individual susceptibility to the effects of the combined treatment may be variable.	none.

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TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX (MCG/ML)	TMAX (H)	λ_z (1/H)	AUC_12H (MCG*H/ML)	T1/2 (H)	MRT (H)	CL/F (L/H/K)	V_z/F (L/K)	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H (%)	2H (%)	12H (%)	CLU/F (L/H/K)	CMAXU (NG/ML)
ELDERLY MALES													
E DOSE)													
001													
002													
003													
005													
006													
016													
MEAN	4.85	0.71	0.52	7.94	1.4	2.23	0.085	0.16	0.09	0.10	0.14	81.42	4.31
S.D.	2.33	0.19	0.15	2.12	0.5	0.50	0.034	0.04	0.01	0.02	0.02	25.25	1.98
GEOMETRIC MEAN	4.20	0.69	0.50	7.65	1.4	2.18	0.080	0.16	0.09	0.10	0.14	78.35	3.82
PLE DOSING)													
001													
002													
003													
005													
006													
016													
MEAN	6.23	0.63	0.41	9.16	2.0	1.94	0.071	0.20	0.10	0.10	0.11	66.31	6.12
S.D.	2.55	0.21	0.15	2.67	1.1	0.23	0.020	0.10	0.02	0.02	0.02	14.78	1.99
GEOMETRIC MEAN	5.86	0.60	0.38	8.86	1.8	1.93	0.069	0.18	0.10	0.10	0.11	65.01	5.86

= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
= 75 YEARS AND OLDER

TABLE F.2
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Drug Interaction Studies (continued)							
792-A-113-US GMR 23511 (Doane)	Open-label, nonrandomized, multiple-dose, PK evaluation of bromfenac and methotrexate in patients with rheumatoid arthritis	**Methotrexate:** 5-15 mg/week days 1 and 8 AND **Bromfenac:** 50 mg q 8 hrs days 4-9	9 (4M, 5F) [2B,1H, 6W]	**Bromfenac:** 50 mg capsule Batch 1TBK W-AR Rouses Point NY March 1991 **Methotrexate:** Patient's own supply (established therapy)	11 June 93	Administration of bromfenac 50 mg q8 hr for 4 days between weekly doses of methotrexate (5-15 mg) appears not to result in clinically significant changes in the PK parameters of methotrexate. The AUC of 7-OH-methotrexate increased by 30% when bromfenac was given. There were no differences in the pharmacokinetics of bromfenac administered simultaneously with methotrexate or 3 days after the weekly dose of methotrexate.	none.

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			Drug Interaction Studies (continued)				
792-A-114-US GMR 23780 (Keane)	Open-label, non randomized, multi-dose PK evaluation of bromfenac and phenytoin, in healthy volunteers	Part 1: Bromfenac 50 mg q 8 hr 4 days Part 2 Phenytoin 300 mg q.d. 7 to 14 days (330 mg in 1 subject) Part 3 Bromfenac AND Phenytoin in above doses 8 days	12 (12M) [1A,1NA, 10W]	Bromfenac 50 mg capsule Batch 1TBK W-AR Rouses Point NY March 1991 Dilantin Parke Davis 30 mg Kapseal NDC 0071-0365-24 Lot No. 56602L 100 mg Kapseal Lot 054D2FA	8 Apr 93	When coadministered with bromfenac, the C_{max} of phenytoin increased by 9% and the AUC increased by 11%. C_{SS} increased by 19% and V_{max} decreased by 5%. Although statistically significant, these changes in phenytoin PK parameters were small. The C_{max} and AUC of bromfenac, when coadministered with phenytoin, were decreased 42%, the Cl/F was increased 100% and the $V_{\lambda z}/F$ were increased 77%.	none.

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			Drug Interaction Studies (continued)				
792-A-116-US GMR 22433 (Mullican)	Open-label, nonrandomized, multiple-dose study of the effect of bromfenac on steady-state serum digoxin concentrations in patients stabilized on digoxin	**Digoxin:** 0.188-0.5 mg/day for days 1-8 AND **Bromfenac:** 50 mg q 8 hrs days 2-8	12 (6M, 6F) [12W]	**Bromfenac** 50 mg capsule Batch 0VTF W-AR Rouses Point NY February 1991 **Digoxin - Patient's own supply (established therapy).**	3 Jan 92	The C_{max} for digoxin was increased significantly (by 19%) following administration of bromfenac. Other PK parameters were not affected. No differences in heart rate, PR interval, QRS interval, and QT interval, were observed following the administration of bromfenac.	none.

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				Food Interaction Studies			
792-A-108-US GMR 22084 (Fruncillo)	Open-label, single-dose, 5-period crossover study of the effects of food, fasting and antacid on bioavailability in healthy volunteers	Bromfenac: single dose 50 mg, fasting 50 mg, 20' before meal 50 mg, immediately after meal 50 mg, 60' after meal 50 mg, fasting, with 30 mL aluminum hydroxide	20 (20M) [4B,Oth, 15W]	Bromfenac 50 mg capsule: Batch 1TKD W-AR Rouses Point NY August 1991 Amphojel Suspension without flavor (aluminum hydroxide) W-A Market Product Control 390028 NDC 0008-0101-01	28 Oct 91	There was no statistically significant difference in AUC when bromfenac was taken under fasting conditions, 20 minutes before a meal, or with antacid. However, the AUC following a meal was reduced by 60%. The C_{max} for bromfenac taken either with a meal or 1 hour after a meal was also significantly (75%) lower than when bromfenac was taken under fasting conditions or 20 minutes before a meal. Unbound bromfenac pharmacokinetic parameters were similarly affected.	none.

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			Food Interaction Studies (continued)				
792-A-118-US GMR 24684 (Fruncillo)	Open-label, single-dose, randomized, 4-period crossover, duration of food effect (high fat meal) on bioavailability in healthy volunteers	Bromfenac 50 mg, fasting 50 mg, 90' after high fat breakfast 50 mg, 150' after high fat breakfast 50 mg, 210' after high fat breakfast	11 (7M,4F) [6B,1H, 4W]	Bromfenac 50 mg capsules Batch 0VTF W-AR Rouses Point, NY February 1991	19 Oct 93	Bromfenac C_{max} and AUC were decreased by 65-75% when given 90 to 210 minutes after a high fat breakfast compared to fasting subjects. No differences in pharmacokinetic parameters were noted between the 3 meal interval groups.	none.

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			Food Interaction Studies (continued)				
AHR-07-US AHR-90-0070 (deDennis)	Open-label, single-dose, 2-period, crossover, pilot study to determine effects of food with and without pretreatment with cimetidine on absorption and systemic availability of bromfenac in healthy volunteers	**Part 1:** **Bromfenac** 50 mg, single dose after overnight fast or immediately after standard breakfast **Part 2:** Pretreated with cimetidine (300 mg x 4 doses in 24 hr) then: **Bromfenac** 50 mg, single dose after overnight fast or immediately after standard breakfast	7 (7M) [5W,2B]	Bromfenac 50 mg capsule Batch 3487 AH Robins Richmond VA March 1985 Tagamet® SmithKline-Beckman market product 1105T13 DOM unknown	31 Dec 85	The mean AUC for fed subjects was 65% lower than that for the fasted subjects. C_{max} was reduced in fed subjects by approximately 79%. Similar decreases due to food were observed when subjects were pretreated with cimetidine.	none.

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			Pharmacokinetics/Pharmacodynamics				
792-A-311-US GMR 24087 (Multicenter)	Patients with pain after oral surgery. Section I: Single-dose, double-blind, placebo-controlled, randomized, parallel, PK/PD Section II: Open-label, single-dose, bioavailability in fed patients Section III: Single-dose, double-blind, placebo-controlled, randomized, parallel, food controlled, PK/PD	Section I: Bromfenac 5,25,50,100, 200 mg Placebo single dose Section II: Bromfenac 50 mg single dose Section III: Bromfenac 50 mg, fed patients 25 mg, fasting patients 25 mg, fed patients placebo single dose	Sections I and III: 154 (71M, 83F) [93W, 36B, 4H, 17A, 4 Oth] Section II: 5 (5M) [4W,1B]	Bromfenac 5 mg capsule Batch 1TKA July 1991 25 mg capsule Batch 0VTE February 1991 50 mg capsule Batch 1TKD August 1991 100 mg capsule Batch 1TKE July 1991 W-AR Rouses Point NY	10 Oct 91	Section I: Plasma concentration and efficacy were dose proportional. But the PK/PD relationship was not well defined. Section III: C_{max} was decreased by 75% and AUC decreased by 52% when bromfenac 25 mg was given with the liquid meal. Efficacy was less affected by the meal (8-hour SPRID reduced by 27%). Both postprandial doses were significantly superior in efficacy to placebo.	none.

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Population Pharmacokinetics							
792-A-303-US GMR 23288 (Multicenter)	Double-blind, multicenter, parallel, randomized, placebo-controlled, in patients with osteoarthritis, population PK, correlation with efficacy. (Plasma samples collected at 1, 2, and 4 weeks.)	Bromfenac 50 mg b.i.d. 25 mg q.i.d. 25 mg b.i.d. Naproxen 500 mg b.i.d. Placebo 6 weeks	211 (74M, 137F) [138W, 26B, 9H, 1A, 3 Oth][a]	Bromfenac 25 mg capsules Batch 0VTE W-AR Rouses Point NY February 1991 50 mg capsules Batch 0VTF W-AR Rouses Point NY February 1991 Naproxen 500 mg capsules Batch 0VTP W-AR Rouses Point NY March 1991 Placebo Batch 0VTH W-AR Rouses Point, NY January 1991	25 Apr 91	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: clearance (Cl/F) = 0.163 L/h/kg (7.4%); volume of distribution (V/F) = 49.0 L; (18.3%); and absorption rate constant (Ka) = 2.81 1/h (24.0%). The estimate of residual error (ε) (%CV) was 0.699 (24.6%). Plots of the change from baseline for each of the four primary efficacy variables versus AUC did not show any apparent relationship. Covariates investigated included age, ethnic origin, gender, weight, and treatment. Only weight was found to influence Cl/F.	none.

a. Ethnic origin was collected retrospectively for this study and was only available for 177 of the 211 included in the analysis.

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Population Pharmacokinetics (continued)							
792-A-306-US GMR 24619 (multicenter)	Double-blind, parallel, randomized, placebo-controlled, population pharmacokinetics, correlation of plasma levels to efficacy, in patients with post-gynecological surgery pain (Plasma samples collected after the 1st dose and 2 hr post-dose on day 2.)	Section 1: Bromfenac 50 mg 100 mg Acetaminophen/ oxycodone 650mg/10 mg Ibuprofen 400 mg Placebo all single dose Section 2: Bromfenac 100 mg Bromfenac 50 mg Acetaminophen/ oxycodone 650mg/10mg Ibuprofen 400 mg all administered (bid) prn, up to 4 doses/day, for up to 5 days.	112 (112F) [15B,3H, 92W,1A, 1Oth]	Bromfenac 50 mg capsules Batch 1TKD August 1991 25 mg capsules Batch 1TKC July 1991 Acetaminophen/ oxycodone 325mg/5 mg capsules Batch 1TKM, 3TAT April 1993 Ibuprofen 200 mg capsules Batch 1TLT July 1991 Placebo Batch 1TKF2 July 1991 W-AR Rouses Point, NY	12 Feb 92	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: Cl/F = 7.0 L/h (11.1%), V/F = 20.9 L (16.4%), Ka = 3.67 l/h (43.8%). The estimate of residual error (ε) was 0.955 (12.8%). The covariates investigated included age, ethnic origin, body weight, and creatinine clearance. None were found to influence either Cl/F or V/F.	none.

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			Population Pharmacokinetics (continued)				
792-A-309-US GMR 24420 (Multicenter)	Double-blind, parallel, randomized, placebo-controlled, population PK, correlation of plasma levels and efficacy, in patients with osteoarthritis. (Plasma samples collected during clinic visits at 1,2, and 4 weeks.)	Bromfenac 50 mg t.i.d. Ibuprofen 600 mg t.i.d. Placebo 4 weeks	100 (23M,77F) [90W,10B]	Bromfenac 25 mg capsule Batch 1TWH Batch 1TWG December 1991 Batch 1VDD April 1992 Batch 0VTE February 1991 Batch 3TGM December 1993 W-AR Rouses Point NY Ibuprofen 300 mg capsule Batch 1TZP W-AR Rouses Point NY February 1992	17 Oct 91	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: Cl/F= 9.82 L/h (8.4%); V/F 31.8 L (14.9%). K_a could not be estimated. The estimate of residual error (ε) was 0.807 (17.4%). The covariates investigated included age, ethnic origin, body weight, and creatinine clearance. None were found to influence either Cl/F or V/F.	none.

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				Other Bioequivalence Studies			
792-A-111-US GMR 20789 (Fruncillo)	Open-label, 2-period crossover, bioequivalence of AH Robins formulation ibuprofen vs. ibuprofen (Motrin®) trade tablets, in healthy volunteers	Ibuprofen single dose AH Robins 400 mg Motrin 400 mg	24 (24M) [4B,1H, 19W]	Ibuprofen 200 mg capsule Batch AHR 4008 AH Robins Richmond, VA Date not available Motrin 400 mg trade tablet NDC No. 0009- 0750-25 The Upjohn Company Kalamazoo, MI Date not available	11 June 1991	The AH Robins capsule formulation of ibuprofen was bioequivalent to the ibuprofen trade tablet (Motrin), with respect to both rate and extent of absorption.	none.

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TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Other Bioequivalence Studies (continued)							
792-A-106-US GMR 20204 (Fruncillo)	Open-label, 3-period crossover, bioequivalence of an Anaprox® ground tablet in capsule form to Synflex® and Anaprox® trade tablets of the same strength, in healthy volunteers	Naproxen sodium single dose ground tablet/capsule 275 mg Synflex® trade 275 mg Anaprox® trade 275 mg	16 (16M) [5B, 10th, 10 W]	Anaprox® ground tablet in capsule form 275 mg Batch 0VWN W-AR Rouses Point, NY November 1990 Synflex® 275 mg trade tablet Syntex Labs. Lmtd. New Zealand Date not available Anaprox® 275 mg trade tablet NDC 18393-274-62 Syntex Lab. Inc. Date not available	5 February 1991	The ground formulation was bioequivalent to the Anaprox and the Synflex trade tablets with respect to both rate and extent of absorption.	none.

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W-AR=Wyeth-Ayerst Research, M=Men, F=Women, A=Asian, B=Black, H=Hispanic, NA=Native American, Oth=Other, W=White, PK=pharmacokinetics, PD=pharmacodynamics, SOM=site of manufacture, DOM=date of manufacture, IV=intravenous, PT=prothrombin time, b.i.d.=twice daily, t.i.d.=three times daily, q.i.d.=four times daily, q.d.=once daily, GMR=Wyeth-Ayerst general medical report, AHR = AH Robins report
All doses were oral unless otherwise specified.

Bromfenac Sodium
NDA 20-535
Reviewer: E.D. Bashaw, Pharm.D.
APW

Wyeth-Ayerst Laboratories
Philadelphia, PA 19101

Submission Date:
~~30~~-Dec.-1994
29

45 Day Filing Review

Background

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID). As such the sponsor is seeking approval of this NDA for use in the management of acute and chronic pain, including the pain of osteoarthritis and primary dysmenorrhea at doses of 25-50mg q6-12 hrs.. The IND for bromfenac was originally submitted to the FDA by A.H. Robins in July 1984. After the corporate acquisition of A.H. Robins by American Home Products, the bromfenac sodium IND was transferred to Wyeth-Ayerst Laboratories in May 1990. At the present time the sponsor has not chosen a tradename for the product.

Application Overview

The pharmacokinetic portion of the NDA (section 6) consists of 95 volumes of data (volumes 1.49-1.144). In this material are the results of 25 in vivo biopharmaceutic studies involving approximately 1000 subjects (352 healthy volunteers, 647 patients). Because of the mass of data this represents the sponsor provided an electronic copy of the data on a laptop computer.

In terms of the general acceptability of the NDA for filing the sponsor has the general number and type of studies in their pk package to allow for a complete evaluation. The sponsor has submitted radiolabeled disposition studies, single and multiple dose studies in both normals and patients with osteoarthritis or dental pain, drug interaction studies, food/fasting studies, and pk/pd studies of the relationship between bromfenac plasma levels and acute pain relief. As part of the filing review 3 of the 25 studies (12%) were randomly chosen for auditing for report completeness and accuracy.

Study Reports Audited

In order to evaluate the completeness of the dataset, 3 of the 25 studies were randomly chosen to be audited by this reviewer. These studies (see Table I, below) represent a basic science study, a demographic study and an interaction study.

Table I.

Study #	Volumes	Short Study Title	# of Subjects
WA792-A-102-US	1.67	Radiolabel Disposition Study	6
WA792-A-104-US	1.97-98	Age and Gender Effects	44
WA792-A-118-US	1.88	Food/Fasting Study	11

WA792-A-102-US 1.67 Radiolabel Disposition Study

This was a study of the metabolic fate of bromfenac in six healthy adult males. Each subject was dosed with a 50mg dose of bromfenac that was radiolabeled with 50uci of ^{14}C. Blood, urine and feces was collected over 96 hours. Results from this study indicated that bromfenac is well absorbed with 80+% of the labeled dose appearing in the urine (66% appearing in the urine in the first 8 hours). Analysis of the urine and fecal material indicated that bromfenac is extensively metabolized. No free bromfenac or bromfenac conjugates were found in the urine. The primary metabolite appeared to be a cyclic amide of bromfenac. Non-compartmental pharmacokinetics were done on the individuals and a mean half-life of 4.54 hrs. was determined.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

WA792-A-104-US 1.97-98 Age and Gender Effects

This study was designed to evaluate the effect of age and gender on the pharmacokinetics of bromfenac. A total of 44 subjects (see Table II, below) were enrolled in this study.

Table II.

Sex	Young*	Young-Elderly**	Elderly***
Males (N=22)	10	6	6
Females (N=22)	10	6	6

*Young = 18-45 yrs old
**Young-Elderly = 65-74 yrs old
***Elderly = 75yrs old

All subjects enrolled in this trial received a single 50mg dose on day 1, followed by 50mg every 12 hours for six doses. On study days 1 and 4, plasma and urine samples were collected for 24 hours to measure bromfenac levels. Samples were analyzed by

The pharmacokinetic results of this study were obtained using noncompartmental pharmacokinetic methods. The plasma half-life for bromfenac in this trial was approximately 1.5-2 hours. This is at variance with the results from the radiolabel study which reports a half-life, albeit determined by radioactivity, of ~4.5 hours. This discrepancy is most likely due to the different methodologies employed, e.g. direct measurement vs. radioactivity. Given the large number of subjects in this trial the 1.5-2 hour estimate of half-life seems to be the appropriate one.

The results of this study indicated that although there were differences related to age, these differences were not thought to be significant by the sponsor. No apparent gender differences were noted. These conclusions were reached using a q12hr dosing interval. Given the 1.5-2 hour half-life of bromfenac, see above, q6hr dosing as allowed by the label would not result in significant accumulation (R for a drug with a 2 hour half-life and q6hr dosing equals 1.14). The sponsor does, however, provide a standard caution regarding the use of this product in patients with hepatic insufficiency. This issue was addressed in the NDA by a study in hepatic impaired individuals.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

WA792-A-118-US 1.88 Food/Fasting Study

This study was designed to evaluate the effect of a high fat meal on the absorption of bromfenac. In addition the study was designed to assess the effect on absorption in relation to the timing of the meal in relation to dosing. The study had a total of four treatment legs:

a.) 50mg of bromfenac in a fasted state
b.) 50mg of bromfenac 1.5 hours after a high fat meal
c.) 50mg of bromfenac 2.5 hours after a high fat meal
d.) 50mg of bromfenac 3.5 hours after a high fat meal

Each leg had a 24 hour wash-out period between legs and all dosing occurred following a 10 hour supervised fast. The high fat meal used was the "FDA High Fat Breakfast" from the 1984 controlled release guidelines.

A total of 12 subjects were enrolled in the trial (8men, 4women). All subjects completed the trial, however, the data from one subject (#6) was excluded from the pharmacokinetic data analysis as this subject had plasma levels below the MQC during dosing leg b (1.5 post-prandial). Plasma samples were obtained for 10hrs. post-dosing.

Samples were analyzed by .

The results of this trial demonstrated that a high fat meal caused a significant decrease in the extent of absorption of bromfenac. This was demonstrated by a decrease in both AUC and Cmax of almost 70%. This effect was consistent through all of the fed treatment legs. The sponsor provided a complete analysis of the data including presentation of Wagner-Nelson data, and MRT in addition to the standard pharmacokinetic parameters.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic

dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

Conclusions

The number and types of studies contained in this NDA are of the general type required. The studies have adequate numbers of subjects and seem appropriately designed. The studies that have been selected from this NDA for auditing are complete and their datasets check with those provided electronically.

Comments

1.) The only criticism of this NDA is that the sponsor needs to provide a better index. The submission of hundreds of pages of statistical and pharmacokinetic data output without an index or dividers is confusing and difficult to deal with from a reviewers standpoint.

Recommendations

While the NDA is fileable from a biopharmaceutic perspective, Comment #1 should be sent to the firm to develop a better index for use by the review staff. As it is presented the provided index is too general to be useful.

E. D. Bash 2/24/95

E. Dennis Bashaw, Pharm.D.
Pharmacokineticist
Pilot Drug Evaluation Staff

Peer Reviewer: Peter Lockwood, M.S. P Lockwood Feb 28 1995

Concur: Ruth E. Stevens, Ph.D.

CC: NDA 20-535 (ORIG),
HFD-007/CSO/ Blatt
HFD-420 (Drug, Chron Files)
HFD-007(Bashaw, Stevens)

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Appendix I-Study Summary Sheets

In Vivo-Pivotal Studies

Supportive Studies-PK

NDA/IND# 20-535 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.67
Study Type Metabolic study - ^{14}C-labeled Study# 792-A-102-US
Study Title A ^{14}C-labeled metabolic disposition study of bromfenac in healthy volunteers

Clinical Investigator	Philip Leese MD	Analytical Investigator	M.Osman
Site	Clinical Research Foundation-America Lenexa, KS	Site	Wyeth-Ayerst Research Princeton, NJ

Single Dose_X Multiple Dose Washout Period
Cross-Over Parallel Other Design
Fasted_X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? _8 Prior to dosing and_4 Post-dosing.
Volunteers_X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	6	6/0	32	18-42	74	58-88

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch #
bromfenac	all	50 mg	capsule		

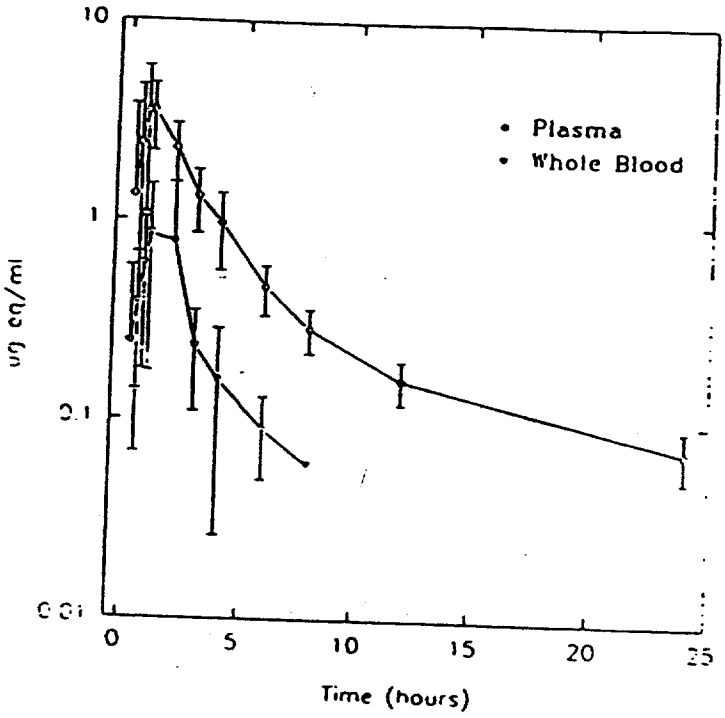
Sampling Times

Plasma	(10 mL) 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 hours postdose
Whole Blood	samples as for plasma
Urine	0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 hours postdose
Feces	through 96 hours postdose
Assay Method	

Labeling Claims From Study

I After the ingestion of [^{14}C] bromfenac sodium, virtually all of the radioactivity in plasma is recovered as unchanged drug.
II. After 24 hours, an average of 80% of the radioactivity has been recovered.
III. Approximately 80% of radioactivity is excreted in the urine; neither unchanged bromfenac nor bromfenac conjugates have been recovered from urine.
IV. A cyclic amide metabolite and four glucuronide conjugates of aglycone metabolites account for most of the radioactivity recovered in the urine.
V. [Tradename] metabolites are eliminated primarily by the kidneys.

Radioactivity concentration in plasma and whole blood following a 50 mg dose of [^{14}C]bromfenac, as the sodium salt



Pharmacokinetic parameters of radioactivity in plasma following oral administration of 50 mg ^{14}C-bromfenac, as the sodium salt

Subject #	C_{max} (µg·equiv/ml)	t_{max} (hr)	AUC (µg·equiv hr/ml)	$t_{1/2}$ (hr)
1				
2				
3				
4				
5				
6				
Mean ± SD	4.87 ± 1.78	1.00 ± 0.52	12.50 ± 2.40	4.54 ± 0.61

Recovery of radioactivity in human urine following a 50 µCi dose of [^{14}C]bromfenac, as the sodium salt

Subject	Percent of dose recovered								
	0-2[a]	2-4	4-8	8-12	12-24	24-48	48-72	72-96	Total
1									
2									
3									
4									
5									
6									
Mean[b]	23.3	26.1	17.1	5.5	6.6	2.9	0.6	0.2	82.4

[a]Hour post-dose
[b]Subjects 1 and 5 were excluded due to unusually low and high recovery, respectively.

Recovery of radioactivity in human feces following a 50 µCi dose of [^{14}C]bromfenac, as the sodium salt

Subject[a]	Percent of dose recovered				
	Day 1	Day 2	Day 3	Day 4	Total
1					
2					
3					
4					
5					
6					
Mean[a]	1.54	4.51	7.78	0.52	13.22

[a]Subjects 1 and 5 were excluded due to unusually high and low radioactivity recovery
[b]No sample

Summary of recovery of radioactivity in humans following a 50 mg dose of [^{14}C]bromfenac, as the sodium salt

Subject	Percent of dose recovered				
	Day 1	Day 2	Day 3	Day 4	Total
2					
3					
4					
6					
Mean[a]	80.2	6.3	8.3	0.8	95.6

NDA/IND# 20-535/ Suppl/Amend.# Submission Date 29 Dec 94 Volume:1.54-1.55
Study Type Absolute bioavailability/Food effect Study# 792-A-107-US
Study Title An absolute bioavailability study of bromfenac (intravenous and oral formulations) in healthy volunteers

Clinical Investigator S Swan MD Analytical Investigator
Site Hennepin County Site
Medical Center
Minneapolis, MN

Single Dose X Multiple Dose Washout Period 2 days
Cross-Over Parallel Other Design Incomplete block design
Fasted X Food Study X FDA High Fat Breakfast X
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
volunteers	24	23/1	31	20-42	75	49-94

Drug Dosage Forms

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg	capsule	49.8 mg	OVTF	
Na citrate	all		diluent		2TJV	
bromfenac	all	50 mg	IV - lyophilized	52.6 mg	2THD	

Sampling Times

Plasma(7mL): IV: 0 ,0.08, 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs post dose
oral: 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hrs post dose
Urine (-)2-0 hrs before dose; 0-12 hrs postdose
Protein Binding 1 hr postdose - equilibrium dialysis

Assay Method:

Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. The mean systemic availability of oral doses of bromfenac administered as [Tradename] as compared with intravenous administration is approximately 67% in humans.

II. Food intake reduces peak plasma concentrations of bromfenac by approximately 75%, while the AUC is reduced by about 60%.

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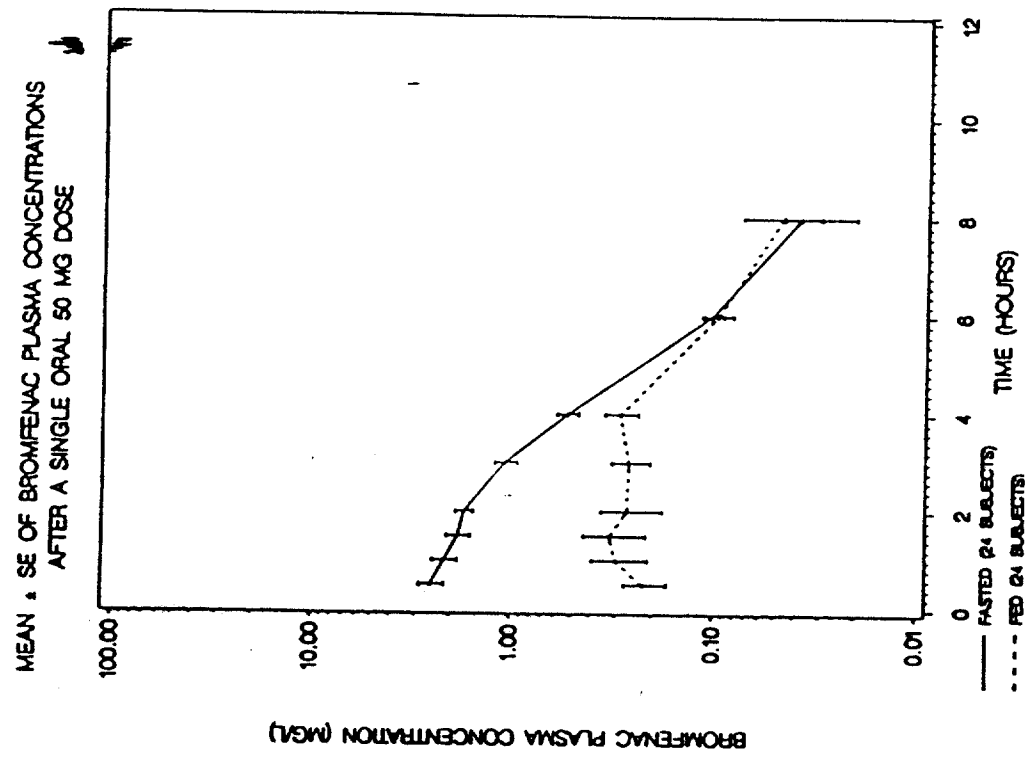
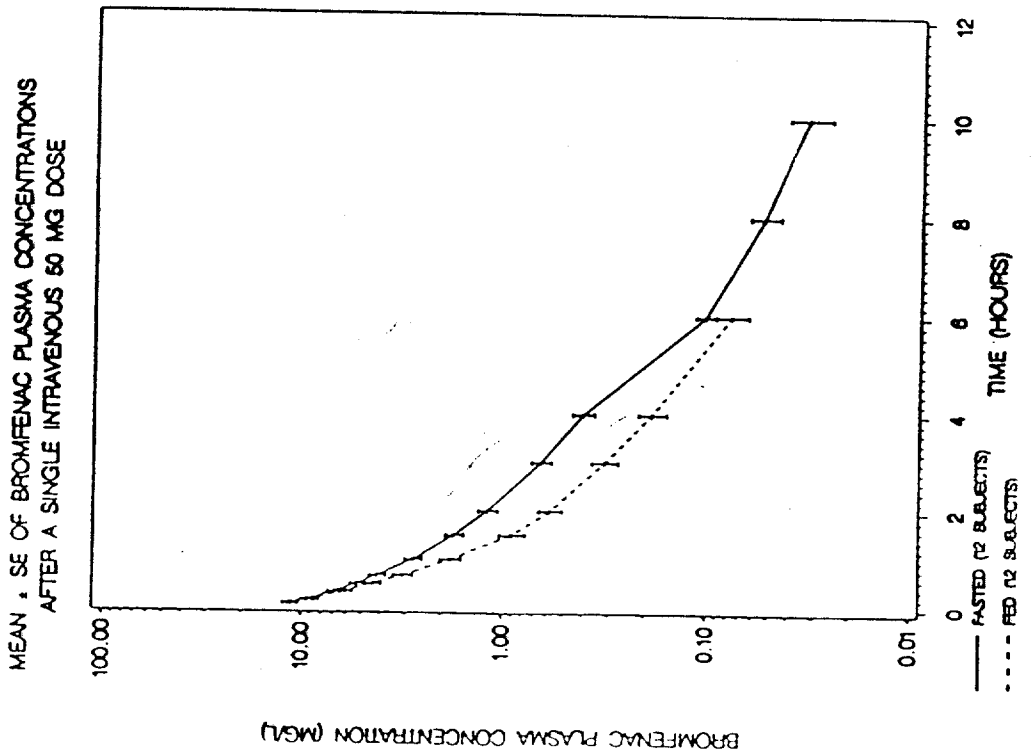
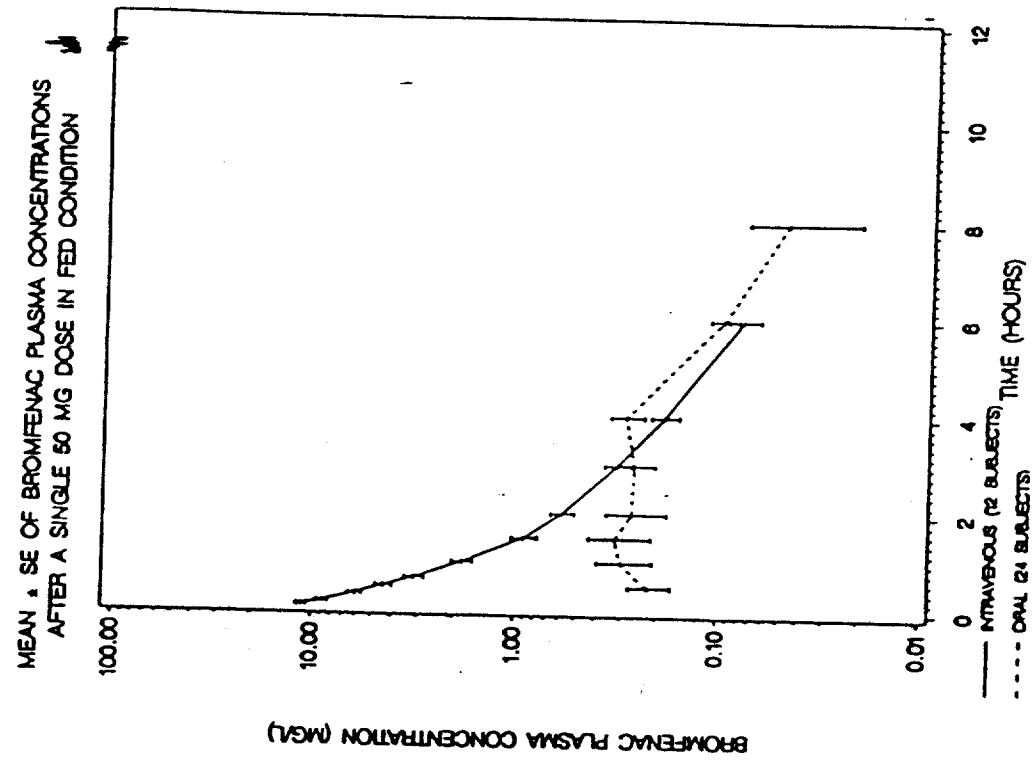






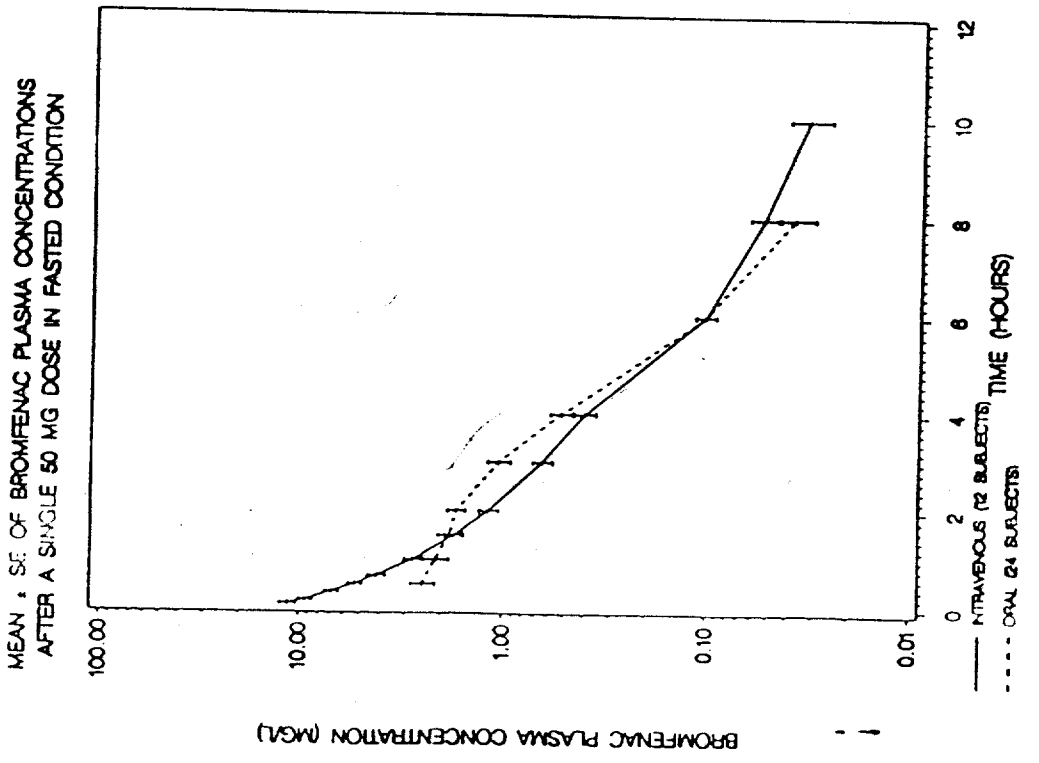


TABLE 6 - STATISTICAL COMPARISONS OF PHARMACOKINETIC PARAMETERS IN HEALTHY VOLUNTEERS RECEIVING A SINGLE 50 MG DOSE OF BROMFENAC

INVESTIGATOR 10713 - SUZANNE K. SWAN, M.D.

SUBJECT	CMAX (MG/L)	TMAX (H)	T1/2 (H)	AUC (MG*H/L)	CL/F* (L/H/K)	V λ_z/F* (L/K)	MRT (H)	λ_z (1/H)	F (%)	FRACTION UNBOUND (%)	AUC,U (MCG*H/ML)	CLR (ML/H)	FRACTION ELIMINATED (%)
INTRAVENOUS FASTED													
MEAN	11.6	0.09	2.5	9.7	0.08	0.2	1.51	0.34	100	0.11	10.4	10	0.17
S.D.	3.1	0.03	1.1	3.0	0.03	0.1	0.36	0.18	0	0.01	3.3	7	0.11
GEOMETRIC MEAN	11.2	0.09	2.3	9.2	0.07	0.2	1.47	0.31	100	0.11	9.9	9	0.17
INTRAVENOUS FED													
MEAN	11.2	0.08	2.0	7.0	0.11	0.3	1.17	0.41	100	0.12	8.1	53	0.60
S.D.	2.1	0.00	1.2	2.4	0.05	0.1	0.35	0.14	0	0.01	2.6	81	0.70
GEOMETRIC MEAN	11.0	0.08	1.8	6.6	0.10	0.3	1.12	0.38	100	0.12	7.8	33	0.46
CAPSULE FASTED													
MEAN	3.3	1.35	1.7	6.5	0.12	0.3	2.28	0.56	67	0.12	7.4	6	0.08
S.D.	1.4	0.87	1.1	2.7	0.04	0.1	0.55	0.27	20	0.02	2.9	6	0.11
GEOMETRIC MEAN	3.1	1.09	1.4	6.1	0.11	0.2	2.22	0.49	64	0.12	7.0	6	0.11
CAPSULE FED													
MEAN	0.6	2.79	1.6	1.7	0.56	1.4	4.03	0.52	27	0.14	2.3	5	0.13
S.D.	0.5	1.85	0.8	1.0	0.31	1.6	1.44	0.26	14	0.01	1.5	8	0.15
GEOMETRIC MEAN	0.4	2.14	1.5	1.4	0.48	1.0	3.78	0.47	24	0.14	2.0	12	0.21

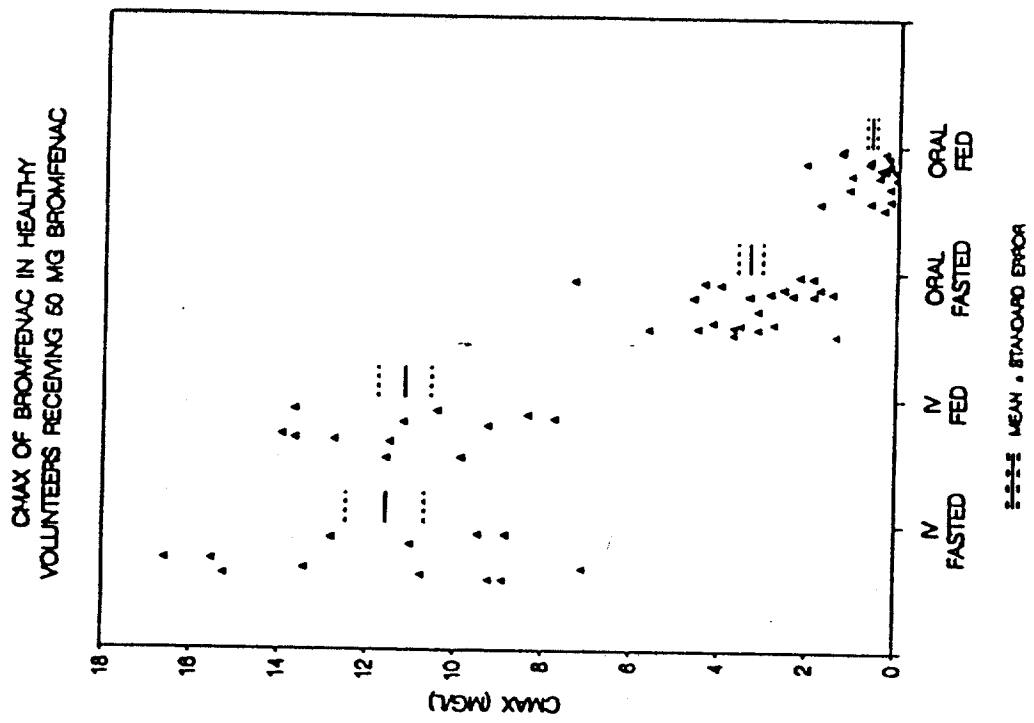
P-VALUES FROM A ONE WAY ANALYSIS OF VARIANCE FOR INTRAVENOUS ADMINISTRATION USING LOG TRANSFORMED DATA

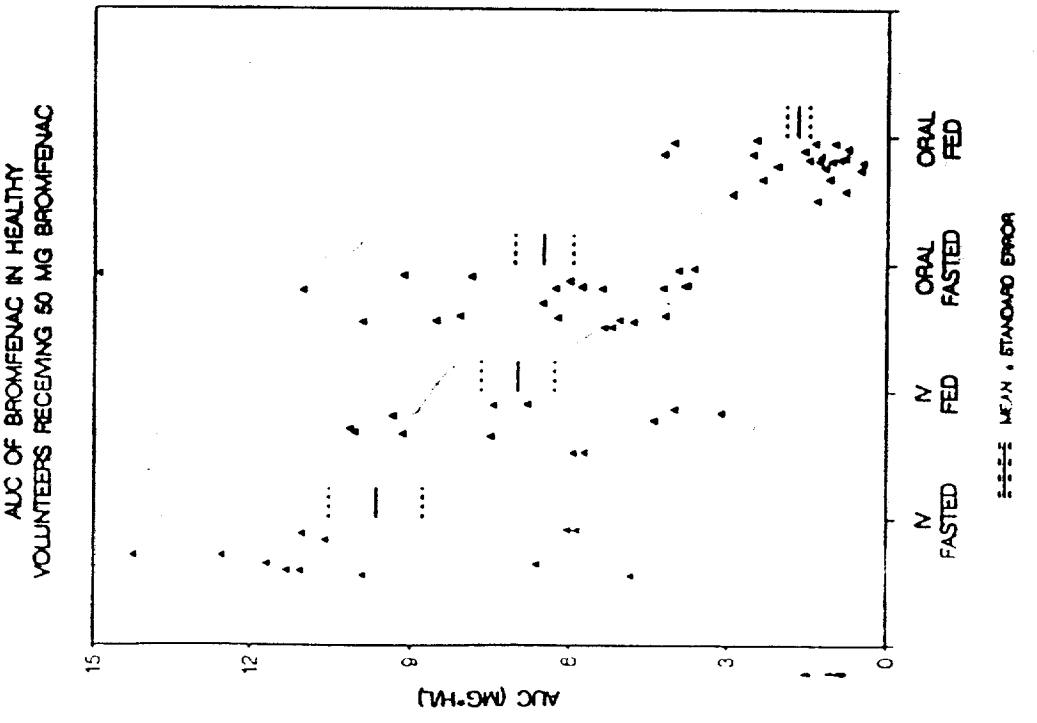
SOURCE OF VARIATION												
DRUG	.83	.33	.25	.04	.02	.30	.02	.25	-	.05	.10	.004	.01

P-VALUES FROM A TWO WAY ANALYSIS OF VARIANCE FOR ORAL ADMINISTRATION USING LOG TRANSFORMED DATA

SOURCE OF VARIATION													
DRUG	.001	.001	.73	.001	.001	.001	.001	.73	.001	.001	.001	.04	-
SUBJECT(SEQUENCE)	.66	.26	.11	.50	.40	.32	.62	.11	-	.01	.32	-	-
SEQUENCE	.13	.54	.48	.04	.19	.38	.40	.48	-	.64	.04	-	.22

NOTE: FOR INTRAVENOUS DOSING, BIOAVAILABILITY (F) IS EQUAL TO 1





NDA/IND# 20-535 ; Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.65
Study Type Dose proportionality Study# 792-A-105-US
Study Title A dose proportionality study of bromfenac following single and multiple-dose administration to healthy male volunteers

Clinical Investigator W Keane MD
Site Drug Evaluation Unit
Hennepin County Med. Center
Minneapolis, MN

Analytical Investigator
Site

Single Dose X Multiple Dose X Washout Period 2 days
Cross-Over X Parallel Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 8 Prior to dosing and 4 Post-dosing.
Healthy X Patients Young Elderly Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age (yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
healthy	24	24/0	28	18-42	75	57-87

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	5 mg (q8h)	capsule	5.01 mg	1TKA	
bromfenac	all	25, 50, 100 mg (q8h)	capsule	25.1 mg	OVTF	

Sampling Times

Plasma: single-dose:0,0.25,0.5,1,2,4,6,8 hrs; multiple-dose: 0,0.17,0.33,0.66,1,1.5,2,3,4,6,8,10,16 hrs
Whole Blood: single-dose: 0.5, 4 hrs post dose; multiple-dose: 0,33, 4 hrs post dose
Urine: pre-dose, 0-2, 2-8, 8-16 hrs postdose (not analyzed)
Protein Binding: 0, 0.33, 2, 6, hrs postdose after multiple dosing - equilibrium dialysis
Assay Method

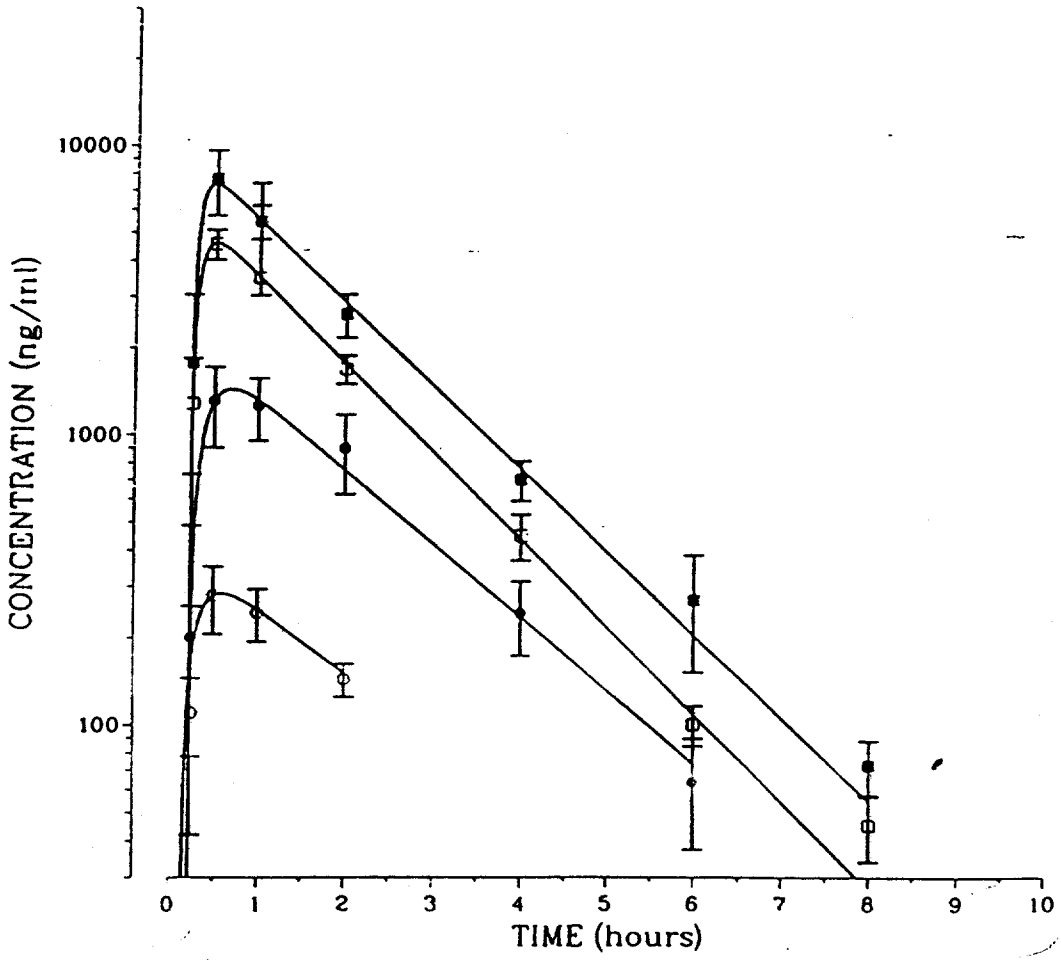
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

1. The dose proportionality based on AUC (area under the plasma-concentration time curve) is linear between doses of 5 and 100 mg.

Figure 1

MEAN ± SE PLASMA CONCENTRATIONS OF BROMFENAC IN SUBJECTS RECEIVING SINGLE 5, 25, 50, OR 100 MG DOSES OF BROMFENAC



○ = 5 MG (n=6)
● = 25 MG (n=6)
□ = 50 MG (n=6)
■ = 100 MG (n=6)

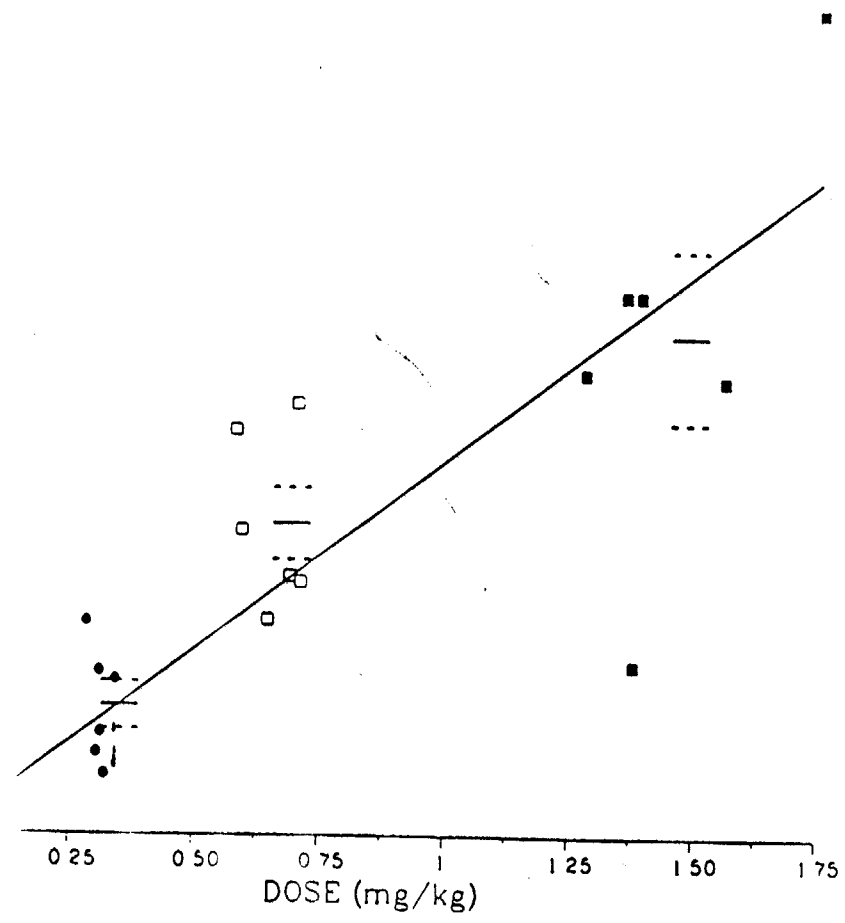
TABLE 4 PHARMACOKINETIC PROFILE OF SINGLE-DOSE BROMFENAC IN HEALTHY MALE SUBJECTS RECEIVING 5, 25, 50, OR 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 10504 WILLIAM F KEANE M D

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC (MCG*H/ML)	AUCI	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)
5	2									
	8									
	12									
	16									
	18									
	24									
	MEAN	0 37	0.79	0.96	0.58	0.48	0 117	0 160	1 89	0 747
	S D	0 09	0.64	0 19	0.08	0 09	0 013	0 024	0 56	0 149
	GEOMETRIC MEAN	0 36	0.63	0.94	0.58	0.47	0 116	0 158	1 83	0 735
25	4									
	7									
	9									
	113									
	19									
	23									
	MEAN	1.86	0.92	1.13	3.29	3 18	0 115	0.181	2.19	0.662
	S.D	0.92	0.58	0.37	1.46	1 46	0 057	0.091	0 79	0 189
	GEOMETRIC MEAN	1.63	0.79	1 09	3.01	2 89	0 104	0 164	2.09	0 637

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC (MCG*H/ML)	AUCI	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)
50	1									
	5									
	10									
	15									
	20									
	22									
	MEAN	4 61	0.58	1 14	7.91	7.82	0 089	0.144	1.82	0 611
	S.D.	1 27	0 20	0 10	2.21	2.19	0 026	0.036	0.19	0 059
	GEOMETRIC MEAN	4 46	0.56	1 14	7.66	7.58	0 085	0 140	1.81	0 609
100	3									
	6									
	111									
	14									
	17									
	21									
	MEAN	7.90	0.58	1.15	12.68	12 54	0 140	0 220	1.89	0 614
	S.D	4.74	0.20	0 15	5.35	5.32	0.087	0 097	0.14	0.089
	GEOMETRIC MEAN	6.84	0.56	1 14	11.52	11 39	0 125	0 206	1.88	0 609

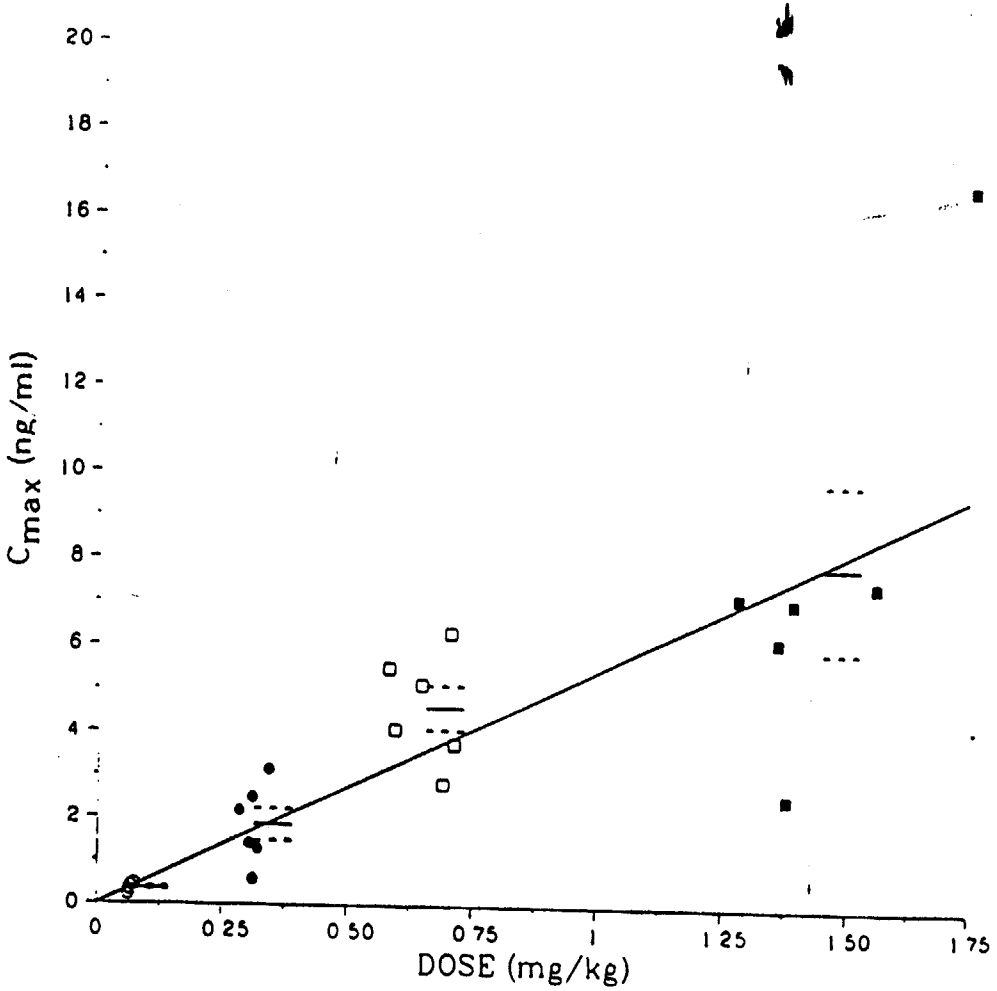
SINGLE DOSE BROMFENAC AUC



5 MG (n=6)
25 MG (n=6)
50 MG (n=6)
100 MG (n=6)

MEAN + SE

SINGLE DOSE BROMFENAC C_{max}

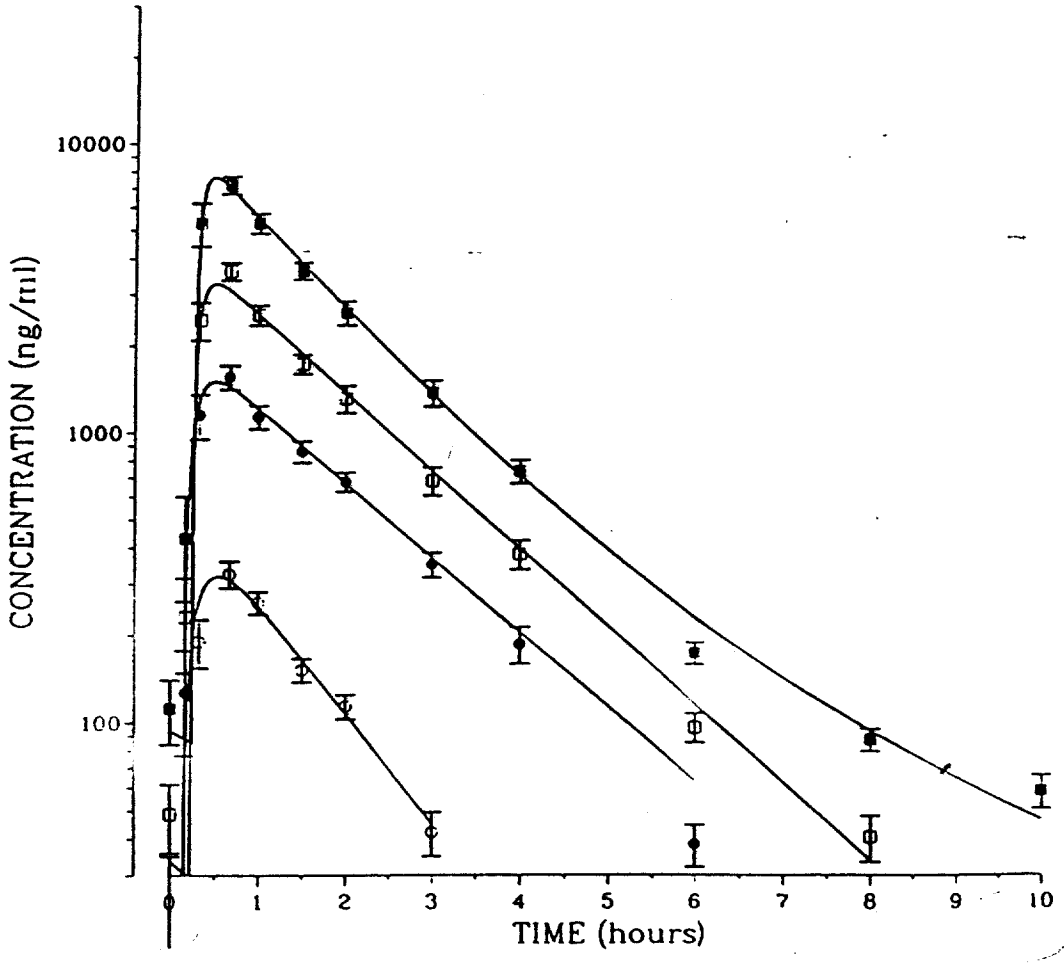


○ = 5 MG (n=6)
● = 25 MG (n=6)
□ = 50 MG (n=6)
■ = 100 MG (n=6)

MEAN + SE

Figure 4

MEAN ± SE PLASMA CONCENTRATIONS OF BROMFENAC
IN 24 SUBJECTS RECEIVING MULTIPLE (Q8H)
5, 25, 50, OR 100 MG BROMFENAC DOSES



o = 5 MG
• = 25 MG
o = 50 MG
■ = 100 MG

TABLE 10 · PHARMACOKINETIC PROFILE OF STEADY-STATE BROMFENAC (OBH) IN HEALTHY MALE SUBJECTS RECEIVING 5, 25, 50, AND 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 10504 WILLIAM F KEANE M D

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC_BH (MCG·H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)
5	1									
	2									
	3									
	4									
	5									
	6									
	7									
	8									
	9									
	10									
	11									
	12									
	13									
	14									
	15									
	16									
	17									
	18									
	19									
	20									
	21									
	22									
	23									
	24									
	MEAN	0 37	0.91	0.95	0.53	1 0	0.150	0 191	1.68	0 844
	S.D.	0 15	0.50	0.36	0 22	-	0.065	0.092	0.36	0.348
	GEOMETRIC MEAN	0.33	0.79	0.89	0 48	1.0	0.138	0 176	1.64	0.782

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUCBH (MCG·H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_BH (NG·H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
25	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
	10															
	11															
	12															
	13															
	14															
	15															
	16															
	17															
	18															
	19															
	20															
	21															
	22															
	23															
	24															
	MEAN	1 85	0 88	1 27	2 89	6 2	0.126	0.208	1 91	0 668	0 14	2 63	4 09	1 0	90 0	147 2
	S D	0 74	0.55	0 72	0 86	3 2	0.040	0.084	0 46	0 245	0 01	1 04	1 24	-	29 4	55 8
	GEOMETRIC MEAN	1 72	0.75	1 13	2 77	5 7	0 120	0.196	1 86	0 614	0 14	2 42	3.91	1 0	85 4	139 1

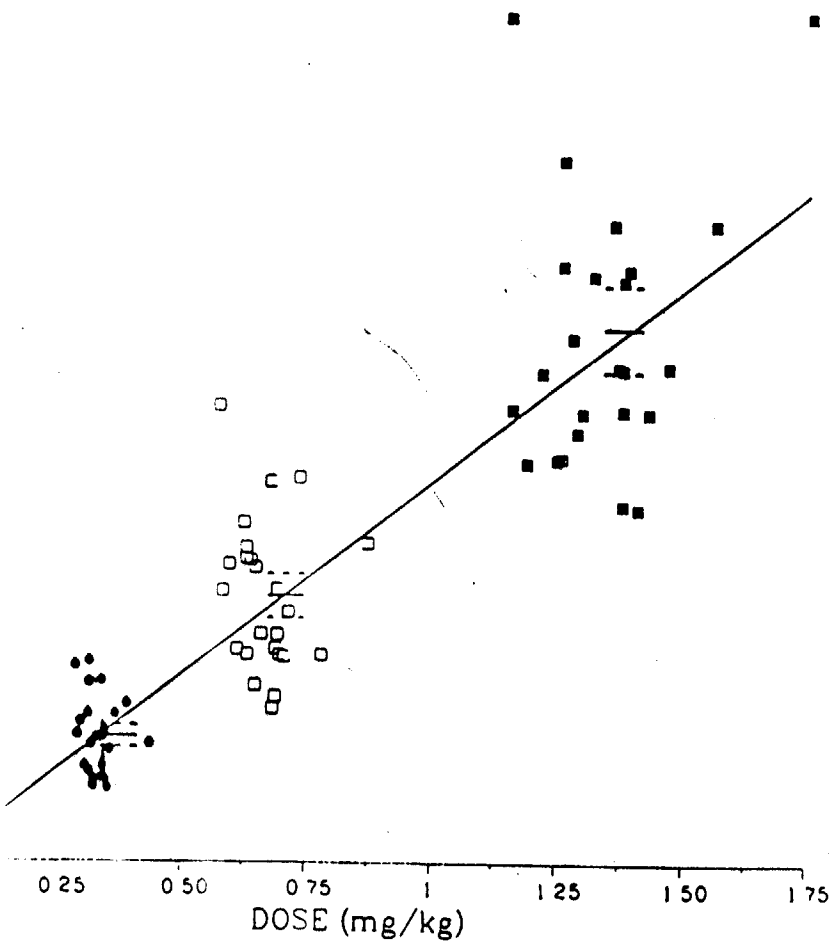
TABLE 10 - PHARMACOKINETIC PROFILE OF STEADY STATE BROMFENAC (OBH) IN HEALTHY MALE SUBJECTS (CONT.)
RECEIVING 5, 25, 50, AND 100 MG ORAL BROMFENAC DOSES

INVESTIGATOR 10504 - WILLIAM F. KEANE, M.D.

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC8H (MCG*H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ_Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_8H (NG*H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
50	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
	10															
	11															
	12															
	13															
	14															
	15															
	16															
	17															
	18															
	19															
	20															
	21															
	22															
	23															
	24															
	MEAN	3.93	0.67	2.14	6.14	13.2	0.118	0.332	1.98	0.380	0.14	5.52	8.53	2.1	86.2	244.4
	S.D.	1.35	0.26	0.85	1.75	5.7	0.035	0.084	0.41	0.157	0.02	2.12	2.59	0.5	29.2	76.6
	GEOMETRIC MEAN	3.70	0.63	1.98	5.92	12.2	0.113	0.322	1.94	0.350	0.14	5.10	8.16	2.1	81.8	233.4

DOSE (MG)	SUBJECT	CMAX (MCG/ML)	TMAX (H)	T1/2 (H)	AUC8H (MCG*H/ML)	R	CL/F (L/H/KG)	VAZ/F (L/KG)	MRT_ORAL (H)	λ_Z (1/H)	FU (%)	CMAXU (NG/ML)	AUCU_8H (NG*H/ML)	RU	CLU/F (L/H/KG)	VAZU/F (L/KG)
100	1															
	2															
	3															
	4															
	5															
	6															
	7															
	8															
	9															
	10															
	11															
	12															
	13															
	14															
	15															
	16															
	17															
	18															
	19															
	20															
	21															
	22															
	23															
	24															
	MEAN	8.24	0.63	2.70	12.31	26.9	0.115	0.434	2.01	0.290	0.14	11.39	17.05	4.3	83.2	314.6
	S.D.	2.96	0.27	1.21	3.16	13.1	0.026	0.185	0.38	0.098	0.01	4.24	4.55	1.1	19.9	135.2
	GEOMETRIC MEAN	7.75	0.58	2.53	11.96	24.7	0.112	0.407	1.97	0.274	0.14	10.69	16.51	4.2	80.9	294.8

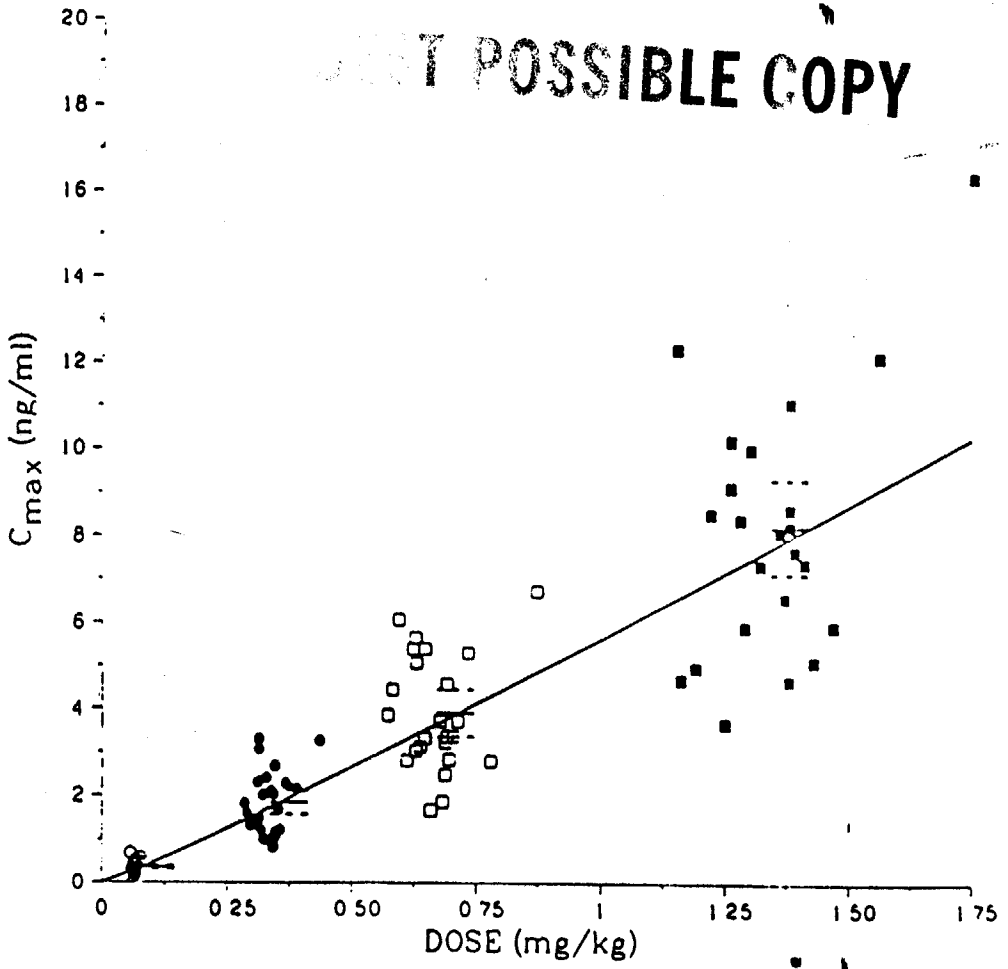
STEADY-STATE BROMFENAC AUC



5 MG (n=24)
25 MG (n=24)
50 MG (n=24)
100 MG (n=24)

MEAN AND 95% CONFIDENCE LIMITS, BASED ON WITHIN-SUBJECT STANDARD DEVIATION

STEADY-STATE BROMFENAC C_{max}



o = 5 MG (n=24)
• = 25 MG (n=24)
o = 50 MG (n=24)
• = 100 MG (n=24)

MEAN AND 95% CONFIDENCE LIMITS, BASED ON WITHIN-SUBJECT STANDARD DEVIATION

NDA/IND# 20-535 Suppl/Amend.# Submission Date 29 Dec 94 Volume 1.97-1.98
Study Type Age/gender Study# 792-A-104-US
Study Title The effects of age and sex on the pharmacokinetics of bromfenac in healthy volunteers

Clinical Investigator P Wicht MD
Site Harris Labs
Clinical Res. Div III
Phoenix, AZ

Analytical Investigator D Hicks
Site Wyeth-Ayerst Res.
Princeton, NJ

Single Dose X Multiple Dose X Washout Period
Cross-Over Parallel X Other Design
Fasted X Food Study FDA High Fat Breakfast
If fasted, how long (hrs.)? 10 Prior to dosing and 4 Post-dosing.
Volunteers X Patients Young X Elderly X Renal Hepatic

Subject Breakdown

Subject Type	N	Male/Female	Mean Age(yr)	Age Range (yr)	Mean Weight (kg)	Weight Range (kg)
young males	10	10/0	29	20-42	82	63-92
young females	10	0/10	29	19-40	61	43-84
young-elderly males	6	6/0	68	65-71	83	78-91
young-elderly females	6	0/6	67	65-68	70	58-76
elderly males	6	6/0	79	75-82	78	68-94
elderly females	6	0/6	81	76-85	63	51-73

Drug Dosage Form

Drug	Treatment Group	Dose	Dosage Form	Strength	Batch No.	Batch Size
bromfenac	all	50 mg (q12h)	capsule	50.4 mg	4023	

Sampling Times

Plasma (10mL) 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 hrs post single dose; also 24 hrs after multiple-dose
Urine collected 0-2, 2-4, 4-8, 8-12 hours postdose - but not analyzed
Protein Binding 0.75, 2, 4, 12 hours postdose - equilibrium dialysis

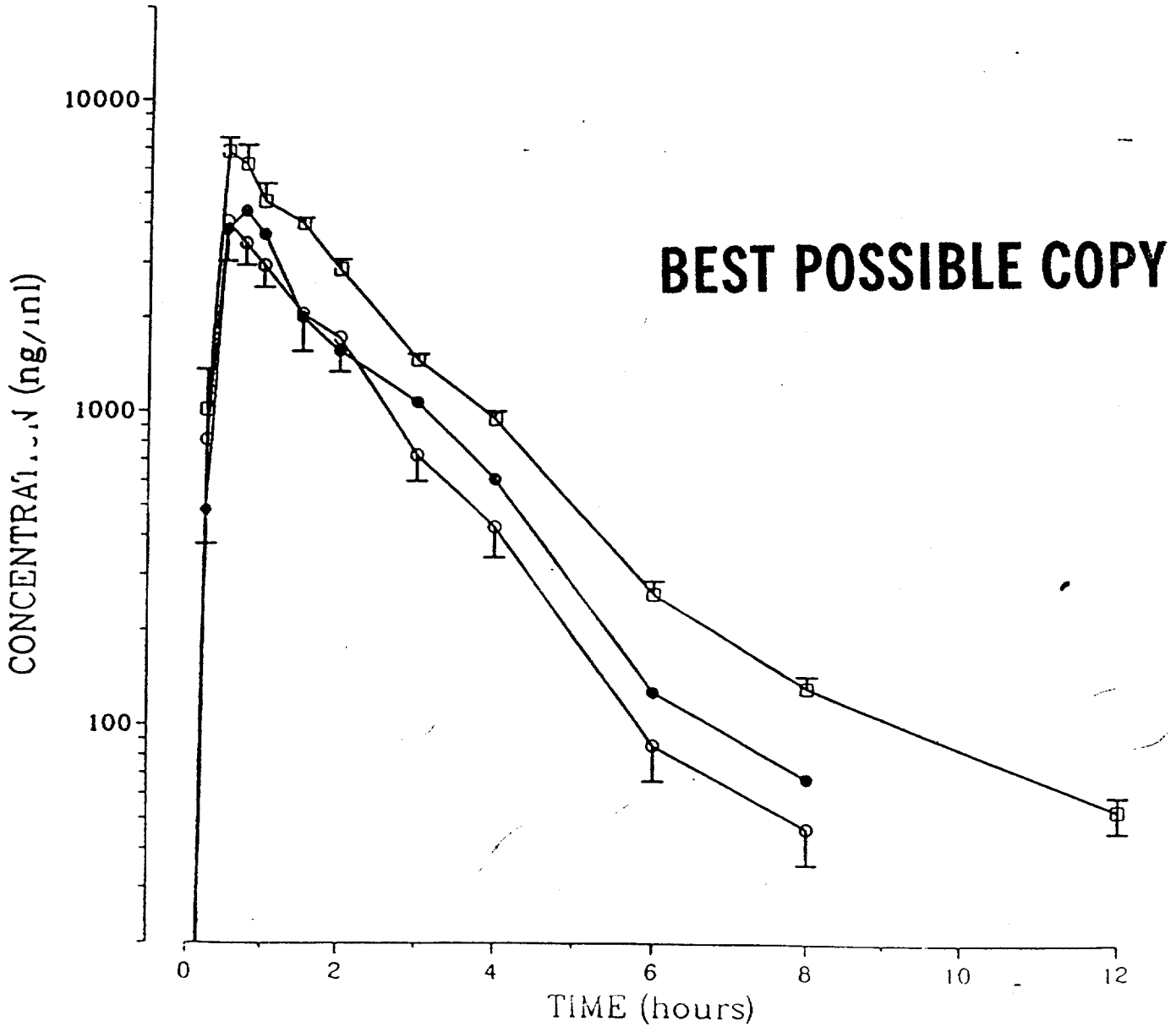
Assay Sensitivity
Assay Accuracy

Labeling Claims From Study

I. No pharmacokinetic differences between males and females.
II. Differences in pharmacokinetics due to age observed but no dosage adjustment for elderly is required.

Figure 1

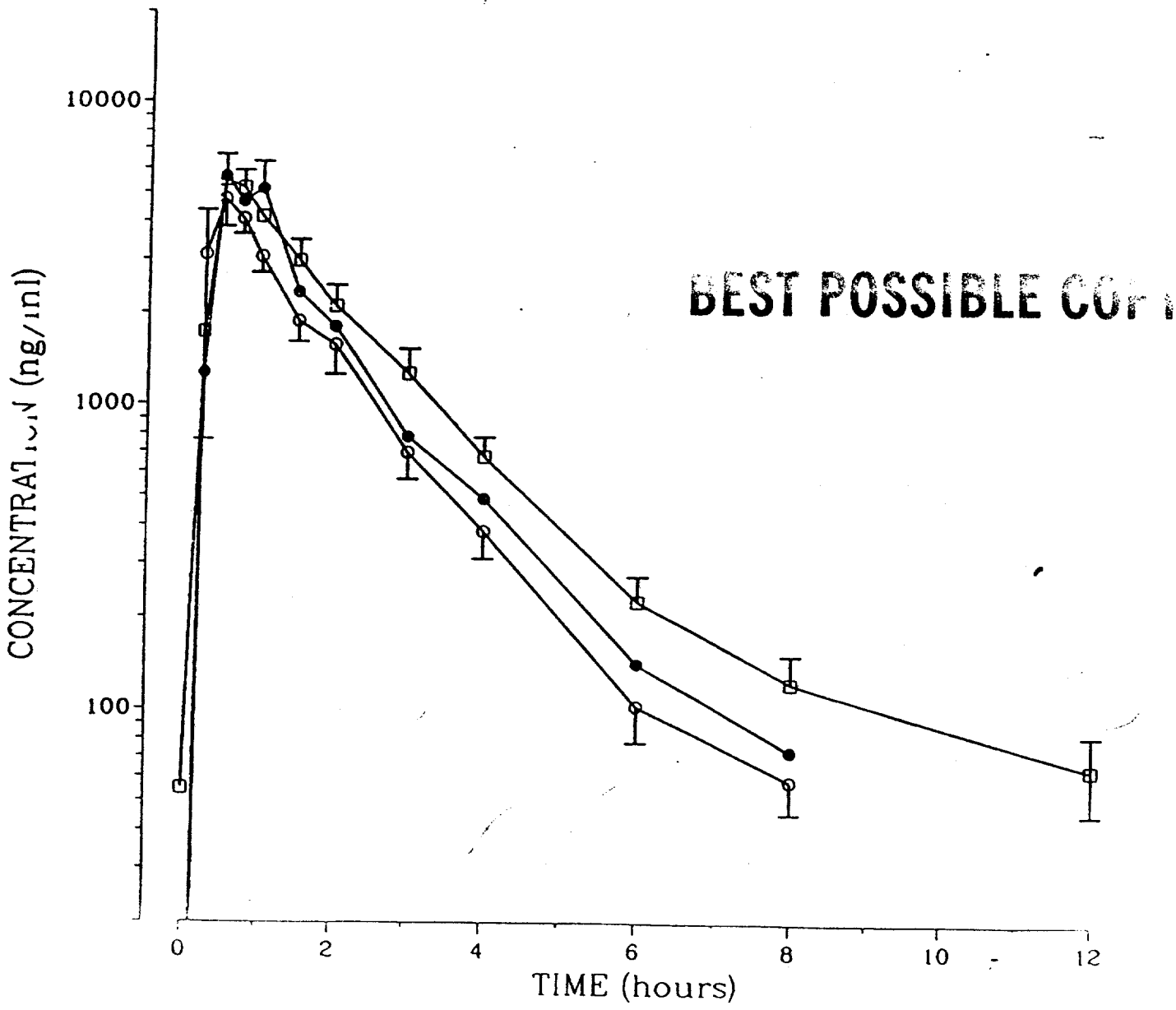
MEAN ± SE OF BROMFENAC PLASMA CONCENTRATIONS
IN THREE GROUPS OF MALE VOLUNTEERS
RECEIVING A SINGLE 50 MG ORAL DOSE OF BROMFENAC



○ = MALE - YOUNG 18-45 yr
● = MALE - YOUNG-ELDERLY 65-74 yr
□ = MALE - ELDERLY 75 yr and older

Figure 3

MEAN ± SE OF PLASMA CONCENTRATIONS OF BROMFENAC
IN THREE AGE GROUPS OF MALE VOLUNTEERS RECEIVING
50 MG ORAL DOSE OF BROMFENAC EVERY 12 HR FOR 4 DAYS



○ = MALE - YOUNG 18-45 yr
● = MALE - YOUNG-ELDERLY 65-74 yr
□ = MALE - ELDERLY 75 yr and older

TABLE 3 - PHARMACOKINETIC PROFILE OF BROMFENAC IN THE PLASMA OF HEALTHY VOLUNTEERS RECEIVING BROMFENAC 50 MG EVERY 12 HOURS (CONT'D)

INVESTIGATOR 10405 - PAUL J. WICHT, M. D.

SUBJECT	CMAX	TMAX	λ_z	AUC_12H	T1/2	MRT	CL/F	V_z/F	PERCENT BROMFENAC UNBOUND IN PLASMA 0.75H	2H	12H	CLU/F	CMAXU
ELDERLY MALES	(MCG/ML)	(H)	(1/H)	(MCG•H/ML)	(H)	(H)	(L/H/K)	(L/K)	(%)	(%)	(%)	(L/H/K)	(NG/ML)
E DOSE)													
001													
002													
003													
005													
006													
016													
MEAN	4.85	0.71	0.52	7.94	1.4	2.23	0.085	0.16	0.09	0.10	0.14	81.42	4.31
S.D.	2.33	0.19	0.15	2.12	0.5	0.50	0.034	0.04	0.01	0.02	0.02	25.25	1.98
GEOMETRIC MEAN	4.20	0.69	0.50	7.65	1.4	2.18	0.080	0.16	0.09	0.10	0.14	78.35	3.82
PLE DOSING)													
001													
002													
003													
005													
006													
016													
MEAN	6.23	0.63	0.41	9.16	2.0	1.94	0.071	0.20	0.10	0.10	0.11	66.31	6.12
S.D.	2.55	0.21	0.15	2.67	1.1	0.23	0.020	0.10	0.02	0.02	0.02	14.78	1.99
GEOMETRIC MEAN	5.86	0.60	0.38	8.86	1.8	1.93	0.069	0.18	0.10	0.10	0.11	65.01	5.86

= 18 TO 45 YEARS
ELDERLY = 65 TO 74 YEARS
= 75 YEARS AND OLDER

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Drug Interaction Studies (continued)				
792-A-113-US GMR 23511 (Doane)	Open-label, nonrandomized, multiple-dose, PK evaluation of bromfenac and methotrexate in patients with rheumatoid arthritis	**Methotrexate:** 5-15 mg/week days 1 and 8 AND **Bromfenac:** 50 mg q 8 hrs days 4-9	9 (4M, 5F) [2B,1H, 6W]	**Bromfenac:** 50 mg capsule Batch 1TBK W-AR Rouses Point NY March 1991 **Methotrexate:** Patient's own supply (established therapy)	11 June 93	Administration of bromfenac 50 mg q8 hr for 4 days between weekly doses of methotrexate (5-15 mg) appears not to result in clinically significant changes in the PK parameters of methotrexate. The AUC of 7-OH-methotrexate increased by 30% when bromfenac was given. There were no differences in the pharmacokinetics of bromfenac administered simultaneously with methotrexate or 3 days after the weekly dose of methotrexate.	none.

W-AR=Wyeth-Ayerst Research, M=Men, F=Women, A=Asian, B=Black, H=Hispanic, NA=Native American, Oth=Other, W=White, PK=pharmacokinetics, PD=pharmacodynamics, SOM=site of manufacture, DOM=date of manufacture, IV=intravenous, PT=prothrombin time, b.i.d.=twice daily, t.i.d.=three times daily, q.i.d.=four times daily, q.d.=once daily, GMR=Wyeth-Ayerst general medical report, AHR = AH Robins report
All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Drug Interaction Studies (continued)				
792-A-114-US GMR 23780 (Keane)	Open-label, non randomized, multi-dose PK evaluation of bromfenac and phenytoin, in healthy volunteers	**Part 1:** Bromfenac 50 mg q 8 hr 4 days **Part 2** Phenytoin 300 mg q.d. 7 to 14 days (330 mg in 1 subject) **Part 3** Bromfenac AND Phenytoin in above doses 8 days	12 (12M) [1A,1NA, 10W]	Bromfenac 50 mg capsule Batch 1TBK W-AR Rouses Point NY March 1991 Dilantin Parke Davis 30 mg Kapseal NDC 0071-0365-24 Lot No. 56602L 100 mg Kapseal Lot 054D2FA	8 Apr 93	When coadministered with bromfenac, the C_{max} of phenytoin increased by 9% and the AUC increased by 11%. C_{SS} increased by 19% and V_{max} decreased by 5%. Although statistically significant, these changes in phenytoin PK parameters were small. The C_{max} and AUC of bromfenac, when coadministered with phenytoin, were decreased 42%, the Cl/F was increased 100% and the $V_{\lambda z}/F$ were increased 77%.	none.

APPEARS THIS WAY

W-AR=Wyeth-Ayerst Research, M=Men, F=Women, A=Asian, B=Black, H=Hispanic, NA=Native American, Oth=Other, W=White, PK=pharmacokinetics, PD=pharmacodynamics, SOM=site of manufacture, DOM=date of manufacture, IV=intravenous, PT=prothrombin time, b.i.d.=twice daily, t.i.d.=three times daily, q.i.d.=four times daily, q.d.=once daily, GMR=Wyeth-Ayerst general medical report, AHR = AH Robins report
All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Drug Interaction Studies (continued)				
792-A-116-US GMR 22433 (Mullican)	Open-label, nonrandomized, multiple-dose study of the effect of bromfenac on steady-state serum digoxin concentrations in patients stabilized on digoxin	**Digoxin:** 0.188-0.5 mg/day for days 1-8 AND **Bromfenac:** 50 mg q 8 hrs days 2-8	12 (6M, 6F) [12W]	**Bromfenac** 50 mg capsule Batch 0VTF W-AR Rouses Point NY February 1991 **Digoxin** - Patient's own supply (established therapy).	3 Jan 92	The C_{max} for digoxin was increased significantly (by 19%) following administration of bromfenac. Other PK parameters were not affected. No differences in heart rate, PR interval, QRS interval, and QT interval, were observed following the administration of bromfenac.	none.

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All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Food Interaction Studies				
792-A-108-US GMR 22084 (Fruncillo)	Open-label, single-dose, 5-period crossover study of the effects of food, fasting and antacid on bioavailability in healthy volunteers	Bromfenac: single dose 50 mg, fasting 50 mg, 20' before meal 50 mg, immediately after meal 50 mg, 60' after meal 50 mg, fasting, with 30 mL aluminum hydroxide	20 (20M) [4B,Oth, 15W]	Bromfenac 50 mg capsule: Batch 1TKD W-AR Rouses Point NY August 1991 Amphojel Suspension without flavor (aluminum hydroxide) W-A Market Product Control 390028 NDC 0008-0101-01	28 Oct 91	There was no statistically significant difference in AUC when bromfenac was taken under fasting conditions, 20 minutes before a meal, or with antacid. However, the AUC following a meal was reduced by 60%. The C_{max} for bromfenac taken either with a meal or 1 hour after a meal was also significantly (75%) lower than when bromfenac was taken under fasting conditions or 20 minutes before a meal. Unbound bromfenac pharmacokinetic parameters were similarly affected.	none.

APPEARS THIS WAY
ON ORIGINAL

W-AR=Wyeth-Ayerst Research, M=Men, F=Women, A=Asian, B=Black, H=Hispanic, NA=Native American, Oth=Other, W=White, PK=pharmacokinetics, PD=pharmacodynamics, SOM=site of manufacture, DOM=date of manufacture, IV=intravenous, PT=prothrombin time, b.i.d.=twice daily, t.i.d.=three times daily, q.i.d.=four times daily, q.d.=once daily, GMR=Wyeth-Ayerst general medical report, AHR = AH Robins report
All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Food Interaction Studies (continued)				
792-A-118-US GMR 24684 (Fruncillo)	Open-label, single-dose, randomized, 4-period crossover, duration of food effect (high fat meal) on bioavailability in healthy volunteers	Bromfenac 50 mg, fasting 50 mg, 90' after high fat breakfast 50 mg, 150' after high fat breakfast 50 mg, 210' after high fat breakfast	11 (7M,4F) [6B,1H, 4W]	Bromfenac 50 mg capsules Batch 0VTF W-AR Rouses Point, NY February 1991	19 Oct 93	Bromfenac C_{max} and AUC were decreased by 65-75% when given 90 to 210 minutes after a high fat breakfast compared to fasting subjects. No differences in pharmacokinetic parameters were noted between the 3 meal interval groups.	none.

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All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Food Interaction Studies (continued)							
AHR-07-US AHR-90-0070 (deDennis)	Open-label, single-dose, 2-period, crossover, pilot study to determine effects of food with and without pretreatment with cimetidine on absorption and systemic availability of bromfenac in healthy volunteers	Part 1: Bromfenac 50 mg, single dose after overnight fast or immediately after standard breakfast Part 2: Pretreated with cimetidine (300 mg x 4 doses in 24 hr) then: Bromfenac 50 mg, single dose after overnight fast or immediately after standard breakfast	7 (7M) [5W,2B]	Bromfenac 50 mg capsule Batch 3487 AH Robins Richmond VA March 1985 Tagamet® SmithKline-Beckman market product 1105T13 DOM unknown	31 Dec 85	The mean AUC for fed subjects was 65% lower than that for the fasted subjects. C_{max} was reduced in fed subjects by approximately 79%. Similar decreases due to food were observed when subjects were pretreated with cimetidine.	none.

W-AR=Wyeth-Ayerst Research, M=Men, F=Women, A=Asian, B=Black, H=Hispanic, NA=Native American, Oth=Other, W=White, PK=pharmacokinetics, PD=pharmacodynamics, SOM=site of manufacture, DOM=date of manufacture, IV=intravenous, PT=prothrombin time, b.i.d.=twice daily, t.i.d.=three times daily, q.i.d.=four times daily, q.d.=once daily, GMR=Wyeth-Ayerst general medical report, AHR = AH Robins report
All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Pharmacokinetics/Pharmacodynamics				
792-A-311-US GMR 24087 (Multicenter)	Patients with pain after oral surgery. Section I: Single-dose, double-blind, placebo-controlled, randomized, parallel, PK/PD Section II: Open-label, single-dose, bioavailability in fed patients Section III: Single-dose, double-blind, placebo-controlled, randomized, parallel, food controlled, PK/PD	Section I: Bromfenac 5,25,50,100, 200 mg Placebo single dose Section II: Bromfenac 50 mg single dose Section III: Bromfenac 50 mg, fed patients 25 mg, fasting patients 25 mg, fed patients placebo single dose	Sections I and III: 154 (71M, 83F) [93W, 36B, 4H, 17A, 4 Oth] Section II: 5 (5M) [4W,1B]	Bromfenac 5 mg capsule Batch 1TKA July 1991 25 mg capsule Batch 0VTE February 1991 50 mg capsule Batch 1TKD August 1991 100 mg capsule Batch 1TKE July 1991 W-AR Rouses Point NY	10 Oct 91	Section I: Plasma concentration and efficacy were dose proportional. But the PK/PD relationship was not well defined. Section III: C_{max} was decreased by 75% and AUC decreased by 52% when bromfenac 25 mg was given with the liquid meal. Efficacy was less affected by the meal (8-hour SPRID reduced by 27%). Both postprandial doses were significantly superior in efficacy to placebo.	none.

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All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Population Pharmacokinetics							
792-A-303-US GMR 23288 (Multicenter)	Double-blind, multicenter, parallel, randomized, placebo-controlled, in patients with osteoarthritis, population PK, correlation with efficacy. (Plasma samples collected at 1, 2, and 4 weeks.)	Bromfenac 50 mg b.i.d. 25 mg q.i.d. 25 mg b.i.d. Naproxen 500 mg b.i.d. Placebo 6 weeks	211 (74M, 137F) [138W, 26B, 9H, 1A, 3 Oth][a]	Bromfenac 25 mg capsules Batch 0VTE W-AR Rouses Point NY February 1991 50 mg capsules Batch 0VTF W-AR Rouses Point NY February 1991 Naproxen 500 mg capsules Batch 0VTP W-AR Rouses Point NY March 1991 Placebo Batch 0VTH W-AR Rouses Point, NY January 1991	25 Apr 91	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: clearance (Cl/F) = 0.163 L/h/kg (7.4%); volume of distribution (V/F) = 49.0 L; (18.3%); and absorption rate constant (Ka) = 2.81 1/h (24.0%). The estimate of residual error (ε) (%CV) was 0.699 (24.6%). Plots of the change from baseline for each of the four primary efficacy variables versus AUC did not show any apparent relationship. Covariates investigated included age, ethnic origin, gender, weight, and treatment. Only weight was found to influence Cl/F.	none.

a. Ethnic origin was collected retrospectively for this study and was only available for 177 of the 211 included in the analysis.

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Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Population Pharmacokinetics (continued)							
792-A-306-US GMR 24619 (multicenter)	Double-blind, parallel, randomized, placebo-controlled, population pharmacokinetics, correlation of plasma levels to efficacy, in patients with post-gynecological surgery pain (Plasma samples collected after the 1st dose and 2 hr post-dose on day 2.)	Section 1: Bromfenac 50 mg 100 mg Acetaminophen/ oxycodone 650mg/10 mg Ibuprofen 400 mg Placebo all single dose Section 2: Bromfenac 100 mg Bromfenac 50 mg Acetaminophen/ oxycodone 650mg/10mg Ibuprofen 400 mg all administered (bid) prn, up to 4 doses/day, for up to 5 days.	112 (112F) [15B,3H, 92W,1A, 1Oth]	Bromfenac 50 mg capsules Batch 1TKD August 1991 25 mg capsules Batch 1TKC July 1991 Acetaminophen/ oxycodone 325mg/5 mg capsules Batch 1TKM, 3TAT April 1993 Ibuprofen 200 mg capsules Batch 1TLT July 1991 Placebo Batch 1TKF2 July 1991 W-AR Rouses Point, NY	12 Feb 92	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: Cl/F = 7.0 L/h (11.1%), V/F = 20.9 L (16.4%), Ka = 3.67 l/h (43.8%). The estimate of residual error (ε) was 0.955 (12.8%). The covariates investigated included age, ethnic origin, body weight, and creatinine clearance. None were found to influence either Cl/F or V/F.	none.

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Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Population Pharmacokinetics (continued)							
792-A-309-US GMR 24420 (Multicenter)	Double-blind, parallel, randomized, placebo-controlled, population PK, correlation of plasma levels and efficacy, in patients with osteoarthritis. (Plasma samples collected during clinic visits at 1,2, and 4 weeks.)	Bromfenac 50 mg t.i.d. Ibuprofen 600 mg t.i.d. Placebo 4 weeks	100 (23M,77F) [90W,10B]	Bromfenac 25 mg capsule Batch 1TWH Batch 1TWG December 1991 Batch 1VDD April 1992 Batch 0VTE February 1991 Batch 3TGM December 1993 W-AR Rouses Point NY Ibuprofen 300 mg capsule Batch 1TZP W-AR Rouses Point NY February 1992	17 Oct 91	The population pharmacokinetic parameter estimates with percent coefficient of variation (%CV) were as follows: Cl/F= 9.82 L/h (8.4%); V/F 31.8 L (14.9%). K_a could not be estimated. The estimate of residual error (ε) was 0.807 (17.4%). The covariates investigated included age, ethnic origin, body weight, and creatinine clearance. None were found to influence either Cl/F or V/F.	none.

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All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
			Other Bioequivalence Studies				
792-A-111-US GMR 20789 (Fruncillo)	Open-label, 2-period crossover, bioequivalence of AH Robins formulation ibuprofen vs. ibuprofen (Motrin®) trade tablets, in healthy volunteers	Ibuprofen single dose AH Robins 400 mg Motrin 400 mg	24 (24M) [4B,1H, 19W]	Ibuprofen 200 mg capsule Batch AHR 4008 AH Robins Richmond, VA Date not available Motrin 400 mg trade tablet NDC No. 0009-0750-25 The Upjohn Company Kalamazoo, MI Date not available	11 June 1991	The AH Robins capsule formulation of ibuprofen was bioequivalent to the ibuprofen trade tablet (Motrin), with respect to both rate and extent of absorption.	none.

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All doses were oral unless otherwise specified.

TABLE F.2
TABLE OF STUDIES

Protocol No. Report No. (Investigator)	Study Design	Dose Frequency, Duration	No. in PK Analysis (gender) [ethnic]	Batch No., Plant, Date Manufactured	IND No., Submission Date of Protocol to Agency	Applicant Conclusion	Agency Comments on Study or Protocol [Date Sent to Sponsor]
Other Bioequivalence Studies (continued)							
792-A-106-US GMR 20204 (Fruncillo)	Open-label, 3-period crossover, bioequivalence of an Anaprox® ground tablet in capsule form to Synflex® and Anaprox® trade tablets of the same strength, in healthy volunteers	Naproxen sodium single dose ground tablet/capsule 275 mg Synflex® trade 275 mg Anaprox® trade 275 mg	16 (16M) [5B, 10Th, 10 W]	Anaprox® ground tablet in capsule form 275 mg Batch 0VWN W-AR Rouses Point, NY November 1990 Synflex® 275 mg trade tablet Syntex Labs. Lmtd. New Zealand Date not available Anaprox® 275 mg trade tablet NDC 18393-274-62 Syntex Lab. Inc. Date not available	5 February 1991	The ground formulation was bioequivalent to the Anaprox and the Synflex trade tablets with respect to both rate and extent of absorption.	none.

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All doses were oral unless otherwise specified.

Bromfenac Sodium
NDA 20-535
Reviewer: E.D. Bashaw, Pharm.D.
APW

Wyeth-Ayerst Laboratories
Philadelphia, PA 19101

Submission Date:
~~30~~-Dec.-1994
29

45 Day Filing Review

Background

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID). As such the sponsor is seeking approval of this NDA for use in the management of acute and chronic pain, including the pain of osteoarthritis and primary dysmenorrhea at doses of 25-50mg q6-12 hrs.. The IND for bromfenac was originally submitted to the FDA by A.H. Robins in July 1984. After the corporate acquisition of A.H. Robins by American Home Products, the bromfenac sodium IND was transferred to Wyeth-Ayerst Laboratories in May 1990. At the present time the sponsor has not chosen a tradename for the product.

Application Overview

The pharmacokinetic portion of the NDA (section 6) consists of 95 volumes of data (volumes 1.49-1.144). In this material are the results of 25 in vivo biopharmaceutic studies involving approximately 1000 subjects (352 healthy volunteers, 647 patients). Because of the mass of data this represents the sponsor provided an electronic copy of the data on a laptop computer.

In terms of the general acceptability of the NDA for filing the sponsor has the general number and type of studies in their pk package to allow for a complete evaluation. The sponsor has submitted radiolabeled disposition studies, single and multiple dose studies in both normals and patients with osteoarthritis or dental pain, drug interaction studies, food/fasting studies, and pk/pd studies of the relationship between bromfenac plasma levels and acute pain relief. As part of the filing review 3 of the 25 studies (12%) were randomly chosen for auditing for report completeness and accuracy.

Study Reports Audited

In order to evaluate the completeness of the dataset, 3 of the 25 studies were randomly chosen to be audited by this reviewer. These studies (see Table I, below) represent a basic science study, a demographic study and an interaction study.

Table I.

Study #	Volumes	Short Study Title	# of Subjects
WA792-A-102-US	1.67	Radiolabel Disposition Study	6
WA792-A-104-US	1.97-98	Age and Gender Effects	44
WA792-A-118-US	1.88	Food/Fasting Study	11

WA792-A-102-US 1.67 Radiolabel Disposition Study

This was a study of the metabolic fate of bromfenac in six healthy adult males. Each subject was dosed with a 50mg dose of bromfenac that was radiolabeled with 50uci of ^{14}C. Blood, urine and feces was collected over 96 hours. Results from this study indicated that bromfenac is well absorbed with 80+% of the labeled dose appearing in the urine (66% appearing in the urine in the first 8 hours). Analysis of the urine and fecal material indicated that bromfenac is extensively metabolized. No free bromfenac or bromfenac conjugates were found in the urine. The primary metabolite appeared to be a cyclic amide of bromfenac. Non-compartmental pharmacokinetics were done on the individuals and a mean half-life of 4.54 hrs. was determined.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

WA792-A-104-US 1.97-98 Age and Gender Effects

This study was designed to evaluate the effect of age and gender on the pharmacokinetics of bromfenac. A total of 44 subjects (see Table II, below) were enrolled in this study.

Table II.

Sex	Young*	Young-Elderly**	Elderly***
Males (N=22)	10	6	6
Females (N=22)	10	6	6

*Young = 18-45 yrs old
**Young-Elderly = 65-74 yrs old
***Elderly = 75yrs old

All subjects enrolled in this trial received a single 50mg dose on day 1, followed by 50mg every 12 hours for six doses. On study days 1 and 4, plasma and urine samples were collected for 24 hours to measure bromfenac levels. Samples were analyzed by

The pharmacokinetic results of this study were obtained using noncompartmental pharmacokinetic methods. The plasma half-life for bromfenac in this trial was approximately 1.5-2 hours. This is at variance with the results from the radiolabel study which reports a half-life, albeit determined by radioactivity, of ~4.5 hours. This discrepancy is most likely due to the different methodologies employed, e.g. direct measurement vs. radioactivity. Given the large number of subjects in this trial the 1.5-2 hour estimate of half-life seems to be the appropriate one.

The results of this study indicated that although there were differences related to age, these differences were not thought to be significant by the sponsor. No apparent gender differences were noted. These conclusions were reached using a q12hr dosing interval. Given the 1.5-2 hour half-life of bromfenac, see above, q6hr dosing as allowed by the label would not result in significant accumulation (R for a drug with a 2 hour half-life and q6hr dosing equals 1.14). The sponsor does, however, provide a standard caution regarding the use of this product in patients with hepatic insufficiency. This issue was addressed in the NDA by a study in hepatic impaired individuals.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

WA792-A-118-US 1.88 Food/Fasting Study

This study was designed to evaluate the effect of a high fat meal on the absorption of bromfenac. In addition the study was designed to assess the effect on absorption in relation to the timing of the meal in relation to dosing. The study had a total of four treatment legs:

a.) 50mg of bromfenac in a fasted state
b.) 50mg of bromfenac 1.5 hours after a high fat meal
c.) 50mg of bromfenac 2.5 hours after a high fat meal
d.) 50mg of bromfenac 3.5 hours after a high fat meal

Each leg had a 24 hour wash-out period between legs and all dosing occurred following a 10 hour supervised fast. The high fat meal used was the "FDA High Fat Breakfast" from the 1984 controlled release guidelines.

A total of 12 subjects were enrolled in the trial (8men, 4women). All subjects completed the trial, however, the data from one subject (#6) was excluded from the pharmacokinetic data analysis as this subject had plasma levels below the MQC during dosing leg b (1.5 post-prandial). Plasma samples were obtained for 10hrs. post-dosing.

Samples were analyzed by

The results of this trial demonstrated that a high fat meal caused a significant decrease in the extent of absorption of bromfenac. This was demonstrated by a decrease in both AUC and Cmax of almost 70%. This effect was consistent through all of the fed treatment legs. The sponsor provided a complete analysis of the data including presentation of Wagner-Nelson data, and MRT in addition to the standard pharmacokinetic parameters.

In general the study was well designed and had sufficient detail. The dataset itself was provided by the sponsor loaded onto a hard drive in a laptop computer. This electronic

dataset was checked with the hard copy of the data in the study report and found to contain no obvious errors.

Conclusions

The number and types of studies contained in this NDA are of the general type required. The studies have adequate numbers of subjects and seem appropriately designed. The studies that have been selected from this NDA for auditing are complete and their datasets check with those provided electronically.

Comments

1.) The only criticism of this NDA is that the sponsor needs to provide a better index. The submission of hundreds of pages of statistical and pharmacokinetic data output without an index or dividers is confusing and difficult to deal with from a reviewers standpoint.

Recommendations

While the NDA is fileable from a biopharmaceutic perspective, Comment #1 should be sent to the firm to develop a better index for use by the review staff. As it is presented the provided index is too general to be useful.

E. Q. Bashaw 2/24/95

E. Dennis Bashaw, Pharm.D.
Pharmacokineticist
Pilot Drug Evaluation Staff

Peer Reviewer: Peter Lockwood, M.S. P Lockwood Feb 28 1995

Concur: Ruth E. Stevens, Ph.D.

CC: NDA 20-535 (ORIG),
HFD-007/CSO/ Blatt
HFD-420 (Drug, Chron Files)
HFD-007(Bashaw, Stevens)

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