CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20535

MEDICAL REVIEW(S)

Bromfenac Single-Dose Analgesia Trials
Synopsis

MEDICAL OFFICER REVIEW

NDA #: 20-535
NAME: Bromfenac Sodium.
SPONSOR: Wyeth-Ayerst Submitted: 12-29-94
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: December 11, 1995.
CSO: C. Koerner

INTRODUCTION:
The sponsor conducted ten single-dose pain trials for this NDA. Six were pain models, and four were surgical pain models. Two of the pain models were closely related: was a dose-finding precursor to the fed-fasted study 311-III. One of the surgical studies, Study 306, was disqualified by DSI after inspection of the largest of the three sites (Dr. Johnson's site). Data on that study are still presented in this report, but results from that site are not considered to contribute toward substantial evidence for any claims.

All of the pain studies were placebo- and active-controlled, randomized, parallel trials, except for one surgical pain trial (Study 20) that had no placebo and two studies (Studie and 311-III) that had no active control. One and two surgical pain studies had multiple-dosing components following the single-dose assessment. Three of the studies, all in surgical pain, were foreign.

The doses of bromfenac ranged from 10 mg to 200 mg. The 25 mg dose was used in all but one study; the 50 mg dose was used in all but two. Doses below 25 mg were employed in four dental studies and just one surgical study. The 200 mg was used in only one dental study. Ibuprofen was an active control in two and two surgical studies; ASA in three studies; and naproxen sodium in one and one surgical study. APAP and ketorolac IM were used in one surgical study each. APAP+oxycodone was used only in the disqualified surgical study.

Observations usually were made at least at baseline, 1/2 hr and hourly thereafter. studies lacked observations between baseline and 1 hour). Pain intensity was rated on a 4-point scale and pain relief was rated on a 5-point scale. Analyses included PID (pain intensity differences from baseline at each observation time), PAR (pain relief at each observation time), PRID (sum of PID and PAR), SPID (cumulative sum of PID at 3 hours or end of study), TOTPAR (cumulative sum of PAR), SPRID (cumulative sum of PRID), and median time to remedication. In the following reviewer's summary assessments, the SPRID over the first three hours was emphasized by the reviewer in making final calls about the relative performance of treatments.

Short narrative summaries of the trials are provided below. The first table of the appendix shows the duration of observation, the number of study sites and the numbers of patients at each dose. The second table summarizes the reviewer's conclusions from each study using 3-hour SPRID as the criterion. The third table provides estimated onset of action times based on 30-minute PRID scores (except for studies 16 and 22 which could only use 1 hour PRIDS). The fourth table shows summarized conclusions about the PRID score at 1 hour. The fifth table shows median time to remedication. Following the tables is are the pages from each study showing that show the PRID results. A compilation of complete sponsor-generated study summaries appears as a separate supplement.

In the summaries and tables the following abbreviations are used:

Bxxx - Bromfenac, dose xxx mg.
Ibuxxx - Ibuprofen, dose xxx mg.
ASA - Aspirin 650 mg.
Nap550 - Naproxen sodium, 550 mg.
APAP - Acetaminophen 1000 mg
APAP+Oxy - Acetaminophen 650 mg with Oxycodone 10 mg.
PL - Placebo.
> - Statistically significantly better than (two-sided $p<.05$).

PAIN MODELS

Study 2: 6 hr.
Rx: B50, B25, B5; ASA; PL.
SPRID (3 hr): Insensitive to ASA. B50, B25, B5 > PL. B50, B25 > ASA. B50 > B5.
ASA failed. B50 and B25 curves were numerically similar. B5 was worse than B50 at 2 hrs and later. B25 peaked at 2 hrs; B50 at 3 hrs. All curves fairly flat in last half of study.

Study 16: 8 hr (no 1/2 hour observation)
Rx: B25, B10, B5; ASA 650; Ibu400; PL.
SPRID (3 hr): All > PL. B25 > ASA 650.
ASA was the lowest of the active treatments numerically. B10 and B5 fell after 2 hours, and were not different from placebo after 4 hours. B25 and Ibu400 curves were similar, peaking at 2-3 hours and falling only slowly thereafter. B25 was numerically > Ibu400, but without statistical differences at any time.

Study 22: 8 hr (no 1/2 hour observation).
Rx: B100, B50, B25, B10; Ibu400; PL.
SPRID (3 hr): All > PL. (B100, B50, B25) > (B5, Ibu 400) > ASA 650.
ASA did poorly. B10 matched Ibu400 for first 2 hours, but fell subsequently. B25 was numerically greatest through 3 hours (peak 2-3 hrs) but then fell faster than the others. B100, B50 and Ibu400 had fairly high, flat arcs, with Ibu400 consistently the numerically smallest of the three..

Study 301: 8 hr.
Rx: B50, B25; Nap 550; PL.
SPRID (3 hr): All > PL. B50, B25 > Nap 550.
No dose-response trend: B25 and B50 looked very similar. Both peaked at 2-3 hours. Peak values were numerically greater than those of Nap 550, but curves crossed over Nap 550 between 6 and 7 hours.

Study 311-I: 8 hr.
Rx: B200, B100, B50, B25, B5; PL. (No active control.)
SPRID (3 hr): B200, B100, B50, B25 > B5.
B5 clearly below the others with rapid fall after peak at 2 hrs. B25 and B50 curves quite similar, peak at 2 hrs. B200 consistently numerically less than B100, but curves similar. B25 and B50 fell more rapidly than B100 & B200; at 6 hrs and latter B25 & B50 were less than B100 and B200, and were not different from placebo.

Study 311-III: 8 hr.
Rx: B50 fed, B25 fasted, B25 fed; PL fed. (No active control, no fasted PL)
SPRID (3 hr): All > PL fed. B25 fasted > B25 fed.
Curves tend to b parallel with B25 fasted on top and B25 fed on bottom, B50 fed between. All curves are atypical, with peak at 4 hours and nearly flat thereafter.

PAIN MODELS SUMMARY

There were 6 pain trials. Study had no active control, and in study 2 ASA did not separate from placebo, however all doses of bromfenac separated from placebo in both studies using the criterion of SPRID over the first 3 hours of the trial. All six studies can be considered adequately sensitive. Based on these trials:

B200 was positive in 1 of 1.
B100 was positive in 2 of 2.
B50 was positive in 4 of 4.
B25 was positive in 6 of 6.
B10 was positive in 2 of 2.
B5 was positive in 3 of 3.

Based on 3-hour SPRID. In fact, the results using 1-hour PRID are almost identical, except that B5 had a statistically significant PRID at 1 hour in only 2 of 3 trials.

B25 was not surpassed (using the 3-hour SPRID or 1-hour PRID criteria) by any higher dose, although higher doses did sometimes beat B25 in the last couple hours. B25 beat ASA 650 in both trials that were sensitive to ASA (as well as in the one where ASA failed). B25 beat Ibu400 in 1 of 2 trials in which they were compared. B25 beat B10 in 1 of 2 trials where they were compared, and B25 beat B5 in 1 of three trials in which they were compared. The median time to remedication with B25 was around 6.5 hours. This was at least 2 hours longer than seen with B10. But increasing the dose to B50

added less than a half hour. The studies were not long enough to assess median remedication time for B100. B100 did not have a greater PRID than B25 until hour 6 in both studies where they were compared.

SURGICAL PAIN MODELS

Study 5: Orthopedic Surgical, 6 hr.
Rx: B25. B10, B5; APAP 1000; PL.
SPRID (3 hr): APAP, B25 > PL.
APAP had broad peak at 1.5 to 2 hours. B25 peaked at 3 hours.

Study 20: Orthopedic Surgical, 6 hr.
Rx: B100, B50, B25; Ibu400, Ibu 200; (no PL).
SPRID (3 hr): B100, Ibu400 > Ibu200.
B50 falls between Ibu 200 and B25. B100 and B25 start below Ibu400, but cross above it between 2 and 3 hrs. B100 fairly flat between 2 and 5 hours.
Sponsor split study on baseline pain. B50 performed poorly in those with severe baseline pain.

Study 302: Orthopedic or Gynecological Surgical, 12 hr;
Rx: B50, B25; Nap 550; Ketorolac 30 mg IM; PL.
SPRID (3 hr): B50, Nap 500, Ketorolac 30 IM > PL.
There was a substantial placebo effect, peaking at 1 hour. Nap 550 had uncharacteristic early peak and rapid fall. No treatment was statistically significant different from PL on 1-hour PRID. Curves for all four active treatments bunched together, peaking at 1-2 hours.

Study 306: Gynecological Surgical or Cesarean, 8 hr.
(*This study was disqualified by DSI)
Rx: B100, B50; APAP+Oxy; Ibu400; PL.
SPRID (3 hr): B100, B50, APAP+Oxy > (Ibu 400, PL).
Substantial placebo effect. Not sensitive for Ibu400. Both B100 and B50 peaked later than APAP+Oxy (3 hrs. vs. 2 hr.) and showed slower fall from peak. B100 numerically greater than B50.

SURGICAL PAIN MODELS SUMMARY

Of the 4 placebo-controlled surgical pain studies, all were adequately sensitive using the criterion of SPRID over the first 3 hours. Although Study 306 was insensitive to ibuprofen 400, it was sensitive to APAP + oxycodone, and both bromfenac doses separated from placebo. Study 20 had no placebo, but a dose-response was seen for ibuprofen. Study 306 was disqualified by DSI, leaving 3 trials that could provide substantial evidence. Of these 3 trials:

B100 was positive in 1 of 1.
B50 was positive in 1 of 1.
B25 was positive in 1 of 2.
B10 was positive in 0 of 1.
B5 was positive in 0 of 1.

B5 and B10 were tried only in surgical study 5, where they both failed. B25 succeeded in 2 of 3 studies, in where it failed it was numerically similar to the others. B100 and B50 were able to beat Ibu400 when it failed in study 306. B100 beat Ibu200 in study 20. Studies 302 and 306, both including gynecological surgery, were distinctive in exhibiting short onset times (at least partly a reflection of the large placebo effects theses studies had) as well as some of the shortest duration of activity. Notably, naproxen did not show its usual sustained activity in study 302.

SUMMARY:
Pooling the studies in the two pain models gives the following by the criterion of 3-hour SPRID:

B200 was positive in 1 of 1.
B100 was positive in 3 of 3.
B50 was positive in 5 of 5.
B25 was positive in 7 of 8.
B10 was positive in 2 of 3.
B5 was positive in 3 of 4.

If one uses the PRID at 1 hour as the criterion, 6 and 2 qualified surgical models were sensitive, and one arrives at the following tally:

B200 was positive in 1 of 1.
B100 was positive in 2 of 2.
B50 was positive in 4 of 5.
B25 was positive in 7 of 7.
B10 was positive in 2 of 3.
B5 was positive in 3 of 4

CONCLUSIONS:
These studies provide substantial evidence for the efficacy of bromfenac sodium in acute analgesic. There is substantial evidence even for the efficacy of a single dose as low as 5 mg. A 25 mg fasted dose appears to be effectively the ceiling dose for acute analgesia. No higher dose was shown to be more effective over the first 3 hours. The 50 mg dose produced PRID curves not much different from the 25 mg dose, and increased the median medication time by only about 1/2 hour (whereas going from 10 to 25 mg extended median remedication time by over 2 hours). Doses of 100 mg or above may be able to extend the period of analgesia, but this appears to be passing into a region of diminishing marginal returns (just as PK models lead us to expect multiplicative dose increases to produce only additive extension of effect).

The onset of analgesia for a 25 mg dose is usually within 30 minutes, which makes it suitable for an acute analgesia indication. The median time to remedication for this dose was more than 6 hours in all but one study. In

one study it was over 8 hours. The data support a dosing interval of at least 6 hours. The suggested interval of up to 12 hours may be too long; the single-dose studies are inadequate to support it.

The fed-fasted study (311-III) showed a significant feeding-effect. From PK studies we know that food reduces absolute bioavailability to less than half of fasting values. In Study 311-III, bromfenac 50 mg fed was shown to have analgesic efficacy, although it was not statistically different from placebo until 1.5 hours. The results of that study were not replicated. Study 311-III together with the PK data support the use of a 50 mg dose if bromfenac is to be given with meals.

Comparisons: Three studies (2, 16 and 22) provided evidence that a 25 mg dose produces superior analgesic effect in dental pain than 650 mg of ASA. The sponsor proposed several other comparative statements for the labeling. Comparisons to APAP 1000, APAP+Oxy, ketorolac, and Ibu 200 were not replicated, and so should not be considered substantiated. Further, APAP+Oxy was compared only in a disqualified study (306). Study 302, which involved ketorolac, had a large placebo response, and all of the active treatments performed very similarly. That suggests that this study lacked upside sensitivity and could not provide much discrimination between analgesics. The comparative evidence from that study should be considered to be weak. B100 and B50 (fasted) were found to beat Ibu400 in two studies (one of which was insensitive to ibuprofen), however, these doses of bromfenac are higher than what should be recommended. Similarly, comparative statements about B5 and B10 seem irrelevant, since 25 mg is the smallest available dose. Statements of "equivalence" in any formal sense have not been statistically documented. B25 seemed to be generally comparable to Ibu400 in the three studies in which they were compared (16, 22 and 302). Likewise B25 was comparable to Nap550 in two studies (301 and 302), although study 302 seemed to lack upside sensitivity.

The proposed labeling claimed that statistical separation from placebo was shown at 30 and 60 minutes. While most studies show B25 PRID separating from placebo at 60 minutes (see above), only study 301 showed this at 30 minutes.

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RECOMMENDATIONS:

The onset of action of bromfenac sodium is short enough (within 30 minutes) to be suitable for an acute analgesia indication. The duration of action appears to be at least 6 hours. The recommended dose should be 25 mg every 6 to 8 hours. Drawing on PK data, a dose of 50 mg might be more appropriate if bromfenac is not given fasted. The labeling should not include the statement that the analgesic effect of bromfenac sodium was statistically greater than placebo at 30 minutes. The labeling may claim that a 25 mg fasted dose was superior to 650 mg aspirin in dental pain models. The labeling may also claim that a 25 mg dose of bromfenac provided analgesia comparable to that of ibuprofen 400 mg or naproxen sodium 550 mg.

John E Hyde

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Pam. Wilmarth 12-26-95

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Bromfenac Single-Dose Studies

Study ID	Pain Model	Hours	No. of Sites	Total N	% Complete	Distribution of Subjects by Treatment															
						B5	B10	B25	B50	B100	B200	B25 fed	B50 fed	ASA 650	Ibu 200	Ibu 400	Nap 550	APAP 1000	Ketorolac 30 IM	APAP + Oxy	PL
2		6	2	202		40		40	41					40							41
16		8	1	269		42	46	45						46		43					45
22		8	1	316			46	44	47	44				44		45					46
301		8&	1	216				36	35								38				107
311- I		8	1	119		21		19	20	19	19										21
311- III	fed & fasted	8	1	80				21				20	20								19
5	Surg	6	1F	157		31	32	31										32			31
20	Surg	6	1F					40	40	40					40	40					0
302	Surg	12&	2F	218				44	43								46		42		43
(306)	Surg	8&	3	238					46	48						48				47	47

F = Indicates foreign study. & = multi-dose study followed the single dose

(306) = Study 306 was disqualified by DSI

B=Bromfenac, APAP=Acetaminophen, ASA=Aspirin, Ibu=Ibuprofen, Nap=naproxen sodium, APAP+Oxy=Acetaminphen 650 mg + Oxycodone 10 mg, PL=Placebo

Bromfenac Single-Dose Studies

Study ID	Pain Model	Hours	3-hour SPRID Results																Comparisons	Notes
			ASA 650	Ibu 200	Ibu 400	Nap 550	APAP 1000	Ketorolac 30 IM	APAP + Oxy	B50 fed	B25 fed	B200	B100	B50	B25	B10	B5			
2		6	-											+	+		+		(B25,50) > ASA, B50>B5	B5,25,50>Pl @ 6hrs in expected order, B25,50 PRID @ 6hr similar to 1 hr values
16		8	+		+										+	+	+		B25> ASA 650	B25 a & Ibu400 stayed above the other after 4 hrs, B25 appreciably different from B10 in terms of duration
22		8	+		+								+	+	+	+			(B25, B50, B100) > (B10, Ibu40) > ASA	B25 had highest SPRID3, Bs correctly ordered after 4 hrs
301		8&				+								+	+				(B50, 25) > Nap550	B25 & B50 curves very similar, B25,50 & Nap nsd at 3 hrs & beyond, Nap crosses @ 6-7 hrs
311- I		8										+	+	+	+		+		(B200, B100, B50, B25) > B5	B25was similar to B50, and B100 was similar to B200. All 4 were simlar through 3-4 hours, after that B25&50 PRIDS fell rapidly, while B100&200 fell slowly. B100 numerically > B200 at 1-8 hrs.
311- II	fed & fasted	8								+	+				+				fasted > B25 fed, B25 fasted numerically > B50 fed at 0.5-7 hrs	
5	Surg	6					+								+	-	-			B10 had dip at 2 hrs
20	Surg	6		*	+*								+*	*	*				(Ibu400, B100, B25) > Ibu200	Agency calculatoins from sponsor's data
302	Surg	12&				+		+						+	-					Substantial placebo response. Atypical naproxen pattern. All active curves were simlar.
(306)	Surg	8&			-				+				+	+					(B100,B50,APAP+Oxy) >Ibu400	Big placebo response. No differences hrs 5-8.
			SPRID=sum Pain Relief (0-5) and Pain Intensity (0-4) Difference Scores																	
			+ = statistically different from placebo; - = not statistically different from placebo.																	
			* No placebo in this group so "-" cannot be assigned, "+" is assigned for beating an active control																	

B=Bromfenac, APAP=Acetaminophen, ASA=Aspirin, Ibu=Ibuprofen, Nap=naproxen sodium, APAP+Oxy=Acetaminphen 650 mg + Oxycodone 10 mg, PL=Placebo

Bromfenac Single-Dose Studies

						Estimated Onset In Minutes															
Study ID	Pain Model	Hours	No. of Sites	Total N	% Complete	B5	B10	B25	B50	B100	B200	B25 fed	B50 fed	ASA 650	Ibu 200	Ibu 400	Nap 550	APAP 1000	Ketorolac 30 IM	APAP + Oxy	PL
2		6	2	202		14		13	14					17							23
16		8	1	269		(39)	(35)	(29)						(41)		(34)					(93)
22		8	1	316			(25)	(18)	(21)	(18)				(35)		(24)					(83)
301		8&	1	216				21	20								23				74
311- I		8	1	119		23		16	14	9	10										39
311- III	fed	8	1	80				35				43	50								57
5	Ortho Surg	6	1F	157		22	20	24										17			28
20	Ortho Surg	6	1F	200				30	25	21					20	16					
302	Surg	12&	2F	218				15	12								14		12		13
(306)	Surg	8&	3	238					12	11						14				9	10

F = indicates foreign study. & = multi-dose study followed the single dose

(306) = Study 306 was disqualified by DSI

( ) = Onset estimated from PRID at 1 hr instead of at 1/2 hour

B=Bromfenac, APAP=Acetaminophen, ASA=Aspirin, Ibu=Ibuprofen, Nap=naproxen sodium, APAP+Oxy=Acetaminophen 650 mg + Oxycodone 10 mg, PL=Placebo

Bromfenac Single-Dose Studies

Study ID	Pain Model	Hours	PRID Results at 1 Hour																Comparisons	Notes
			ASA 650	Ibu 200	Ibu 400	Nap 550	APAP 1000	Ketorolac 30 IM	APAP + Oxy	B50 fed	B25 fed	B200	B100	B50	B25	B10	B5			
2		6	-											+	+		+		B50 > ASA	
16		8	+		+										+	+	+			based on 1 hr PRID
22		8	+		+								+	+	+	+			(B100,50,25)>(B10,ASA), Ibu > ASA	No 1/2 hr recording for onset estimated, based on 1 hr PRID
301		8&				+								+	+				B25 > Nap	
311- I		8										+	+	+	+		-		(B200,100,50,25) > B5	
311- III	fed	8													+				B25 fasted > B25 fed	
5	Ortho Surg	6					+								+	-	+			
20	Ortho Surg	6		*	+								*	*	*				Ibu400> (B50,B25, Ibu200)	Agency calculations from sponsor data
302	Surg	12&				-		-						-	-					Failed trial--Substantial placebo response
(306)	Surg	8&			-				-				+	-					B100 > Ibu 400	Substantial placebo response
			PRID=sum Pain Relief (0-5) and Pain Intensity (0-4) Difference Scores																	
			+ = statistically different from placebo; - = not statistically different from placebo.																	

B=Bromfenac, APAP=Acetaminophen, ASA=Aspirin, Ibu=Ibuprofen, Nap=naproxen sodium, APAP+Oxy=Acetaminophen 650 mg + Oxycodone 10 mg, PL=Placebo

Bromfenac Single-Dose Studies

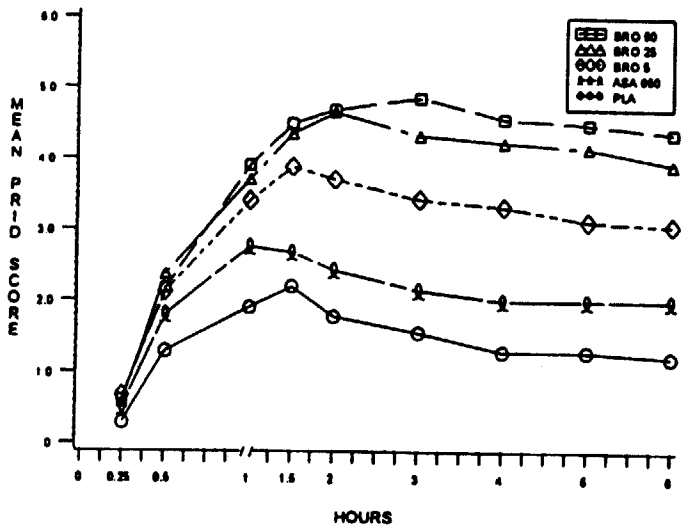
						Duration in Hours (Time until 50% Remedicate)															
Study ID	Pain Model	Hours	No. of Sites	Total N	% Complete	B5	B10	B25	B50	B100	B200	B25 fed	B50 fed	ASA 650	Ibu 200	Ibu 400	Nap 550	APAP 1000	Ketorolac 30 IM	APAP + Oxy	PL
2		6	2	202		>6		>6	>6					2.7							1.7
16		8	1	269		3.7	3.7	6.4						3.3		5.4					2.2
22		8	1	316			4.4	6.5	7.0	>8				3.4		5.8					2.0
301		8&	1	216				6.1	6.4								6.0				2.0
311-I		8	1	119		3.8		6.1	6.0	>8	>8										2.0
311-III	fed & fasted	8	1	80				>8				>8	>8								2.2
5	Ortho Surg	6	1F	157		4.6	5.2	>6										4.2			2.6
20	Ortho Surg	6	1F					>6	>6	>6					4.1	5.4					
302	Surg	12&	2F	218				2.3	3.0								2.7		3.5		1.7
(306)	Surg	8&	3	238					4.6	6.0						3.0				4.2	2.5

F = indicates foreign study. & = multi-dose study followed the single dose

(306) = Study 306 was disqualified by DSI.

B=Bromfenac, APAP=Acetaminophen, ASA=Aspirin, Nap=naproxen sodium, APAP+Oxy=Aceatinophen 650 mg + Oxycodone 10 mg, PL=Placebo

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID

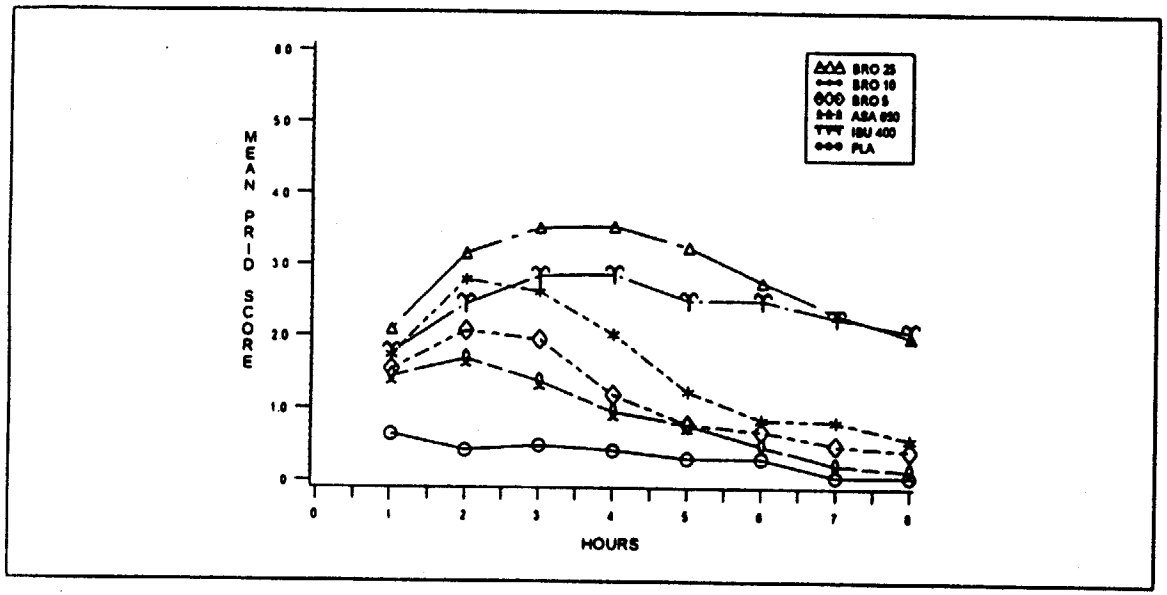
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	41	11.10 A	24.76 A	5.10 A
Bromfenac 25 mg	40	10.71 AB	23.21 AB	4.75 AB
Bromfenac 5 mg	40	9.09 BC	18.79 BC	4.10 BC
Aspirin 650 mg	40	6.41 CD	12.48 CD	3.38 CD
Placebo	41	4.72 D	8.70 D	2.63 D
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		5.6530	12.7212	2.3253

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours) 1/4	1/2	1	1 1/2	2	3	4	5	6
Bromfenac 50 mg	0.61 (1.09) 41	2.17 (1.76) 41	3.90 (1.83) 40 A (d)	4.49 (2.16) 39 A	4.68 (2.18) 36 A	4.85 (2.21) 36 A	4.56 (2.45) 36 A	4.49 (2.62) 34 A	4.37 (2.69) 33 A
Bromfenac 25 mg	0.58 (1.26) 40	2.38 (2.16) 40	3.70 (2.41) 39 AB	4.35 (2.52) 38 A	4.65 (2.46) 34 AB	4.33 (2.65) 32 AB	4.23 (2.78) 30 AB	4.15 (2.83) 29 AB	3.93 (2.74) 28 AB
Bromfenac 5 mg	0.68 (1.46) 40	2.13 (2.13) 40	3.40 (2.42) 40 AB	3.88 (2.42) 37 AB	3.70 (2.74) 32 BC	3.43 (2.82) 27 BC	3.33 (2.90) 25 BC	3.13 (2.94) 24 BC	3.08 (2.89) 22 BC
Aspirin 650 mg	0.50 (1.13) 40	1.80 (1.80) 40	2.75 (2.36) 38 BC	2.68 (2.49) 36 BC	2.43 (2.62) 29 CD	2.15 (2.59) 23 CD	2.00 (2.61) 17 CD	2.00 (2.73) 17 CD	2.00 (2.69) 16 CD
Placebo	0.29 (0.93) 41	1.29 (1.87) 41	1.90 (2.39) 39 C	2.20 (2.75) 32 C	1.78 (2.55) 21 D	1.56 (2.39) 14 D	1.29 (2.27) 12 D	1.29 (2.28) 11 D	1.22 (2.21) 11 D
p-value Trt (b)	0.620	0.111	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Investigator (b)	0.601	0.511	0.841	0.823	0.921	0.526	0.535	0.533	0.424
p-value Trt*Baseline (c)	0.240	0.872	0.314	0.310	0.164	0.246	0.126	0.143	0.108
Root MSE (b)	1.172	1.899	2.246	2.420	2.447	2.482	2.553	2.633	2.607

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + error
(c) Model: PRID = u + T(i) + I(j) + TI(ij) + B(I)(jk) + TB(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AN PEAK PRID [a]

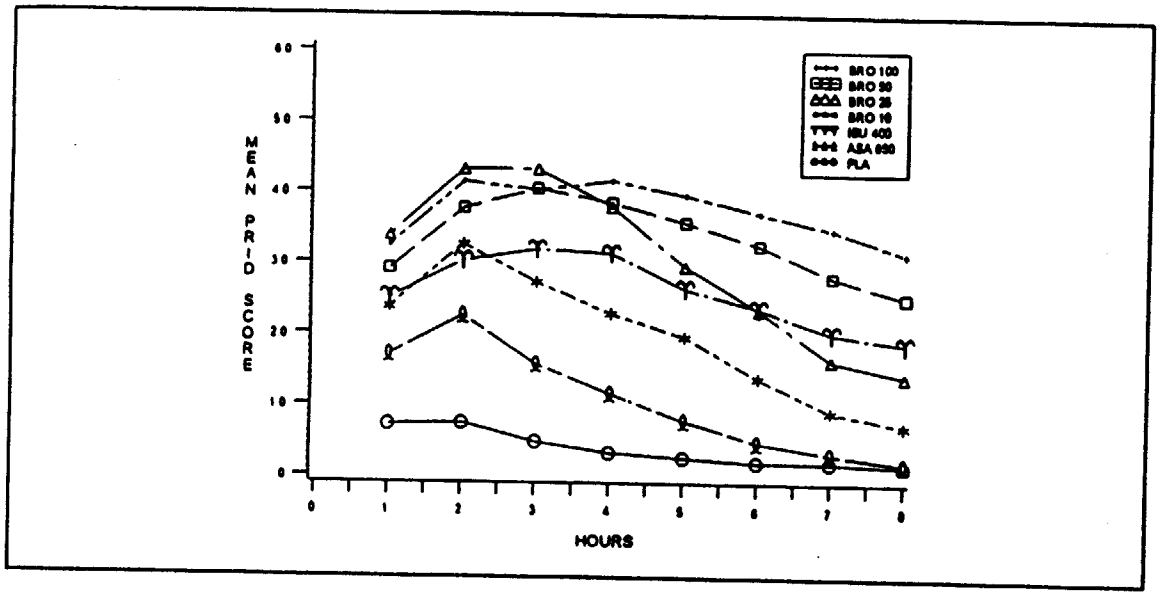
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 25 mg	45	7.00A	21.60A	4.15A
Bromfenac 10 mg	46	5.83AB	12.36B	3.35AB
Bromfenac 5 mg	42	4.60AB	8.95B	2.50BC
Aspirin 650 mg	46	3.82B	7.03BC	2.20C
Ibuprofen 400 mg	43	5.63AB	18.17A	3.72A
Placebo	45	1.31C	2.70C	0.93D
Prob > F		0.0001	0.0001	0.0001
Root MSE		4.5183	11.814	2.2752

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)															
Treatment	1		2		3		4		5		6		7		8	
Bromfenac 25 mg	2.09 45 (a)	(1.88) A(d)	3.16 45	(2.43) A	3.51 33	(2.69) A	3.53 32	(2.68) A	3.24 26	(2.75) B	2.76 23	(2.78) A	2.31 17	(2.66) A	2.00 14	(2.59) A
Bromfenac 10 mg	1.74 46	(2.27) A	2.78 44	(2.44) A	2.61 34	(2.59) AB	2.02 21	(2.35) B	1.24 17	(1.92) B	0.85 10	(1.79) B	0.83 8	(1.83) B	0.59 8	(1.50) B
Bromfenac 5 mg	1.55 42	(1.78) A	2.07 40	(2.08) AB	1.95 25	(2.11) BC	1.19 18	(2.10) BC	0.79 8	(1.73) B	0.69 5	(1.76) B	0.50 3	(1.44) B	0.43 2	(1.38) B
Aspirin 650 mg	1.44 44	(1.93) A	1.69 39	(2.27) A	1.38 26	(2.15) C	0.96 15	(2.06) C	0.78 8	(1.88) B	0.49 4	(1.47) B	0.22 2	(0.97) B	0.16 1	(0.90) B
Ibuprofen 400 mg	1.77 43	(2.13) A	2.44 40	(2.25) AB	2.84 33	(2.53) AB	2.86 27	(2.54) A	2.49 21	(2.59) A	2.49 19	(2.66) A	2.26 20	(2.62) A	2.07 17	(2.68) A
Placebo	0.64 45	(1.68) B	0.42 41	(1.44) C	0.49 15	(1.42) D	0.42 6	(1.29) C	0.31 3	(1.40) B	0.31 2	(1.36) B	0.07 1	(0.45) B	0.07 1	(0.45) B
p-value Trt (b)	0.036		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.353		0.675		0.379		0.868		0.898		0.961		0.695		0.677	
Root MSE (b)	1.909		2.082		2.164		2.094		1.976		1.921		1.717		1.639	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + Surdose + error
(c) Model: PRID = PR = u + T(i) + B(j) +TB(ij) + Surdose + error
Surdose = Time from end of surgery to dose.
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

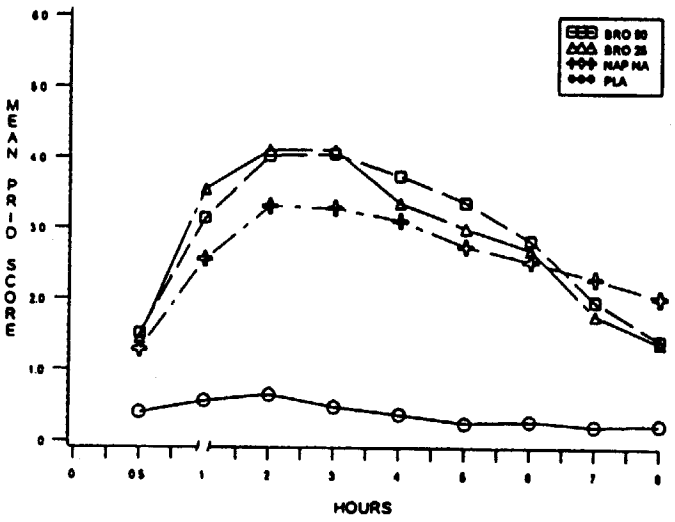
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 100 mg	44	9.40A	28.27A	5.16A
Bromfenac 50 mg	47	8.70A	25.47AB	4.49AB
Bromfenac 25 mg	44	9.86A	23.45AB	4.86AB
Bromfenac 10 mg	46	6.99B	15.25C	4.13B
Ibuprofen 400 mg	45	7.12B	19.78BC	3.98B
Aspirin 650 mg	44	4.74C	8.34D	2.77C
Placebo	46	1.70D	2.99E	1.30D
p-value		<0.0001	<0.0001	<0.0001
Root MSE of Ranks		77.80	75.25	77.8712

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)															
	1		2		3		4		5		6		7		8	
Bromfenac 100 mg	3.25 44 (a)	(1.79) A (d)	4.14 42	(1.92) A	4.02 38	(2.05) AB	4.16 38	(2.24) A	3.95 36	(2.35) E	3.70 30	(2.45) A	3.48 24	(2.58) A	3.14 20	(2.69) A
Bromfenac 50 mg	2.91 47	(2.09) A	3.77 46	(2.30) AB	4.04 38	(2.31) A	3.85 38	(2.44) AB	3.57 32	(2.64) AB	3.26 26	(2.74) AB	2.81 22	(2.62) A	2.51 17	(2.63) AB
Bromfenac 25 mg	3.39 44	(1.73) A	4.32 44	(1.64) A	4.32 41	(1.97) A	3.80 40	(2.00) AB	2.95 32	(2.28) BC	2.34 26	(2.33) C	1.64 19	(2.45) BC	1.41 10	(2.38) CD
Bromfenac 10 mg	2.37 46	(1.66) BC	3.26 43	(1.88) BC	2.72 35	(2.10) C	2.28 28	(2.56) C	1.96 18	(2.66) D	1.38 14	(2.25) D	0.91 11	(2.04) CD	0.72 8	(1.81) DE
Ibuprofen 400 mg	2.50 44	(1.95) AB	3.02 43	(2.07) CD	3.19 36	(2.25) BC	3.13 33	(2.53) B	2.63 24	(2.70) CD	2.36 17	(2.70) BC	2.01 13	(2.63) B	1.87 11	(2.59) BC
ASA 650 mg	1.70 44	(2.09) C	2.25 43	(2.49) D	1.57 23	(2.13) D	1.16 18	(2.08) D	0.77 12	(1.87) E	0.48 8	(1.56) E	0.32 3	(1.34) D	0.18 3	(0.95) E
Placebo	0.72 45	(1.60) D	0.74 39	(1.68) E	0.48 14	(1.44) E	0.33 6	(1.38) D	0.26 3	(1.02) E	0.20 2	(0.93) E	0.20 2	(0.93) D	0.15 2	(0.73) E
p-value Trt (b)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Baseline (c)	0.019		0.337		0.451		0.496		0.360		0.175		0.621		0.949	
p-value Trt*Site (c)	0.692		0.793		0.898		0.795		0.681		0.832		0.749		0.974	
Root MSE of Ranks (b)	80.367		78.97		76.072		75.315		75.035		71.58		69.967		68.146	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + S(k) +TB(ij) + error
(c) Model: PRID = u + T(i) + B(j) +S(k) + TB(ij) + TS(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) (Intent-to-Treat Patients) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)



3-HOUR AND FINAL SPRID AND PEAK PRID [a]

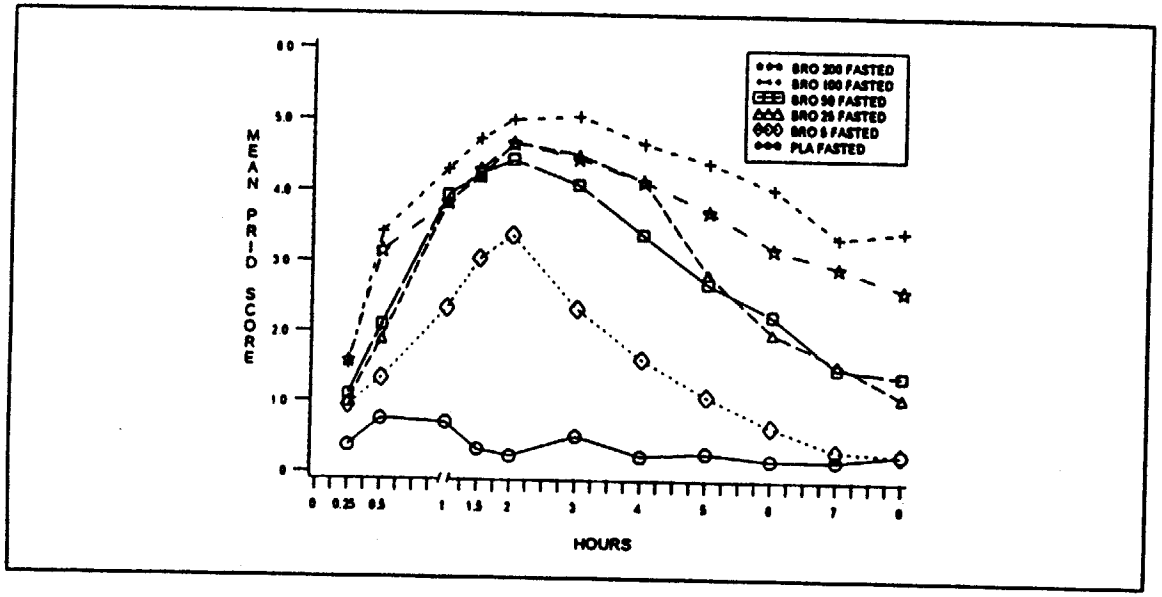
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	35	9.17 A	23.83 A	4.94 A
Bromfenac 25 mg	36	9.56 A	23.14 A	4.67 AB
Naproxen Na 550 mg	38	7.52 B	20.84 A	3.92 B
Placebo	106	1.52 C	3.01 B	1.25 C
Overall treatment p-value		0.0001	0.0001	0.0001
Root MSE		3.7736	11.1258	1.7222

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)								
	1/2	1	2	3	4	5	6	7	8
Bromfenac 50 mg	1.51 (1.67) 34 (a) A (d)	3.14 (2.03) 34 AB	4.03 (2.04) 34 A	4.06 (2.52) 27 A	3.74 (2.81) 24 A	3.37 (2.72) 20 A	2.83 (2.64) 17 A	1.97 (2.42) 10 A	1.43 (2.24) 9 A
Bromfenac 25 mg	1.44 (1.56) 36 A	3.56 (2.02) 36 A	4.11 (1.72) 36 A	4.11 (1.95) 32 A	3.36 (2.39) 26 A	3.00 (2.59) 20 A	2.69 (2.34) 18 A	1.78 (2.34) 12 A	1.39 (2.26) 9 A
Naproxen Na 550 mg	1.29 (1.59) 38 A	2.55 (1.78) 38 B	3.32 (2.05) 35 B	3.29 (2.20) 28 A	3.11 (2.32) 25 A	2.74 (2.40) 22 A	2.53 (2.54) 17 A	2.29 (2.52) 13 A	2.03 (2.56) 9 A
Placebo	0.41 (1.03) 106 B	0.57 (1.25) 105 C	0.65 (1.40) 74 C	0.48 (1.32) 20 B	0.38 (1.20) 14 B	0.25 (0.96) 8 B	0.28 (1.11) 6 B	0.22 (0.94) 4 B	0.24 (1.03) 4 B
p-value Trt (b)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (c)	0.724	0.887	0.614	0.179	0.307	0.173	0.070	0.302	0.296
Root MSE (b)	1.318	1.598	1.669	1.835	1.974	1.946	1.945	1.839	1.806

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + error
(c) Model: PRID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Section I Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) (Valid-for-Efficacy Patients)



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 200 mg, fasted	19	11.41A	29.01AB	5.42A
Bromfenac 100 mg, fasted	19	12.47A	33.26A	5.37A
Bromfenac 50 mg, fasted	20	10.55A	23.15B	4.85A
Bromfenac 25 mg, fasted	19	10.76A	24.16B	5.11AB
Bromfenac 5 mg, fasted	21	7.13B	12.15C	4.00B
Placebo, fasted	21	1.35C	2.65C	1.52C
p-value		0.0001	0.0001	0.0001
Root MSE		4.4794	12.127	1.7136

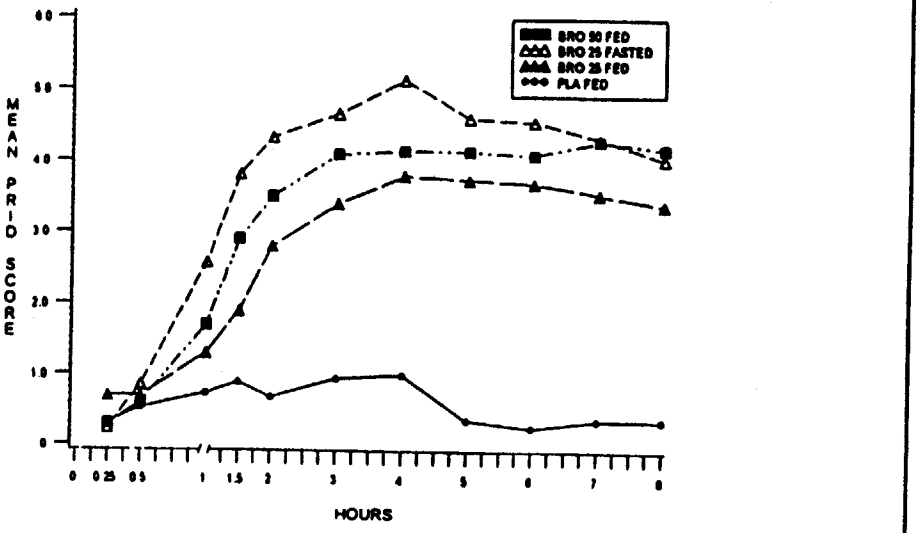
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)											
	0.25	0.5	1	1.5	2	3	4	5	6	7	8	
Bromfenac 200 mg, fasted	1.58 (1.74) 19 (a)	3.16 (1.89) 19 A (c)	3.84 (1.77) 19 A	4.32 (1.86) 19 AB	4.68 (1.34) 19 A	4.47 (1.81) 18 A	4.16 (2.17) 17 A	3.74 (2.66) 17 AB	3.21 (2.55) 14 AB	2.95 (2.48) 13 AB	2.63 (2.48) 12 AB	
Bromfenac 100mg, fasted	1.53 (1.81) 19	3.42 (1.84) 19 A	4.32 (1.92) 19 A	4.74 (2.13) 19 A	5.00 (2.08) 19 A	5.05 (2.01) 17 A	4.68 (1.92) 17 A	4.42 (2.01) 17 A	4.05 (2.22) 17 A	3.37 (2.27) 15 A	3.47 (2.48) 14 A	
Bromfenac 50 mg, fasted	1.10 (1.25) 20	2.10 (1.52) 20 AB	3.95 (1.88) 20 A	4.25 (1.94) 20 A	4.45 (2.14) 20 A	4.10 (2.40) 17 A	3.40 (2.48) 17 A	2.70 (2.41) 13 B	2.25 (2.57) 12 C	1.50 (2.37) 9 C	1.40 (2.28) 6 BC	
Bromfenac 25 mg, fasted	1.00 (1.56) 19	1.89 (1.85) 19 AB	3.84 (1.74) 19 A	4.21 (1.78) 19 AB	4.68 (1.80) 19 A	4.53 (2.17) 17 A	4.16 (2.29) 17 A	2.84 (2.54) 16 BC	2.00 (2.49) 11 BC	1.58 (2.17) 8 BC	1.11 (1.91) 6 BC	
Bromfenac 5 mg, fasted	0.95 (1.69) 21	1.33 (1.62) 21 B	2.33 (1.62) 21 B	3.05 (2.09) 21 B	3.38 (1.94) 21 B	2.33 (2.37) 17 B	1.62 (2.58) 14 B	1.10 (1.89) 8 CD	0.67 (1.15) 6 C	0.33 (0.91) 5 C	0.29 (0.72) 3 C	
Placebo, fasted	0.38 (1.24) 21	0.76 (1.67) 21 B	0.71 (1.98) 21 B	0.33 (2.01) 21 C	0.24 (1.84) 21 C	0.52 (1.47) 4 B	0.24 (0.89) 2 B	0.29 (1.10) 2 D	0.19 (1.12) 2 C	0.19 (0.87) 1 C	0.29 (1.31) 1 C	
p-value Trt (b)	0.270	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
p-value Trt*Baseline (b)	0.210	0.349	0.381	0.539	0.047	0.134	0.527	0.838	0.660	0.855	0.806	
Root MSE (b)	1.538	1.720	1.822	1.979	1.816	1.995	2.097	2.141	2.062	1.949	1.941	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + B(j) + TB(ij) + error

Figure 7, Table 9. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Section III Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg, fed	20	7.28AB	28.13AB	4.60AB
Bromfenac 25 mg, fasted	21	9.16A	32.18A	5.33A
Bromfenac 25 mg, fed	20	5.84B	24.04B	3.95B
Placebo, fed	19	2.08C	4.74C	1.47C
p-value		0.0001	0.0001	0.0001
Root MSE		4.2618	13.046	2.0123

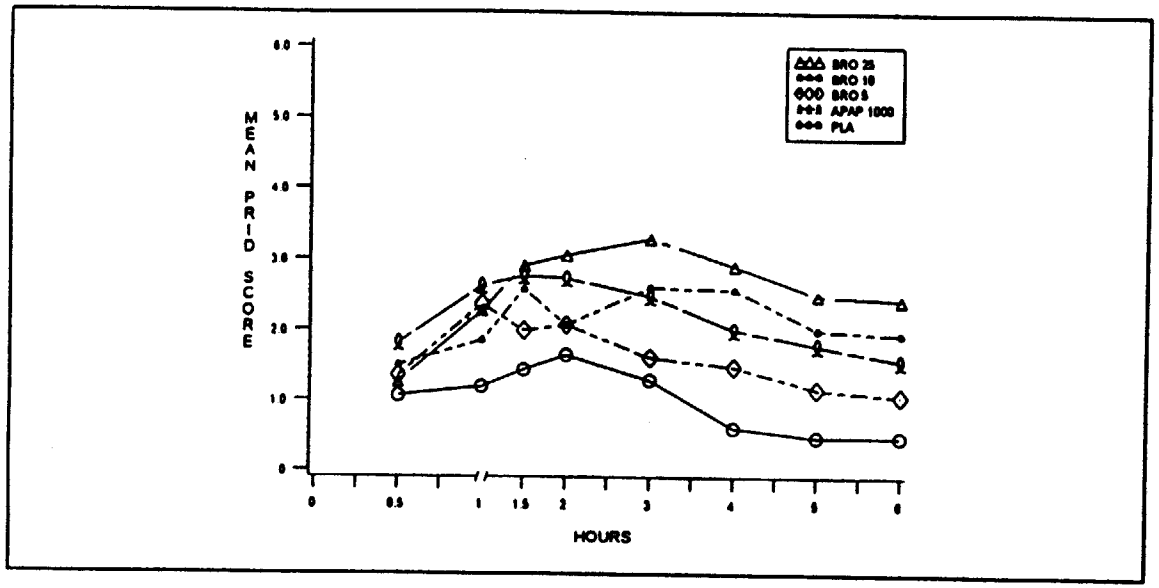
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)										
	0.25	0.5	1	1.5	2	3	4	5	6	7	
Bromfenac 50 mg, fed	0.30 (0.92) 20 (a)	0.60 (1.10) 20	1.70 (1.87) 20 AB (c)	2.90 (2.07) 20 AB	3.50 (1.91) 20 AB	4.10 (1.97) 18 AB	4.15 (2.08) 17 AB	4.15 (2.08) 17 A	4.10 (2.22) 17 A	4.30 (2.43) 16 A	4.20 (2.44) 16 A
Bromfenac 25 mg, fasted	0.24 (1.00) 21	0.86 (1.49) 21	2.57 (1.89) 21 A	3.81 (1.57) 21 A	4.33 (1.02) 21 A	4.67 (1.28) 21 A	5.14 (1.15) 21 A	4.62 (1.66) 21 A	4.57 (1.83) 20 A	4.33 (1.98) 19 A	4.05 (2.01) 19 A
Bromfenac 25 mg, fed	0.70 (1.53) 20	0.70 (1.53) 20	1.30 (1.98) 20 B	1.90 (2.43) 20 BC	2.80 (2.61) 20 B	3.40 (2.60) 15 B	3.80 (2.73) 14 B	3.75 (2.67) 14 A	3.70 (2.68) 14 A	3.55 (2.65) 14 A	3.40 (2.76) 14 A
Placebo, fed	0.32 (1.00) 19	0.53 (1.31) 19	0.74 (1.45) 19 B	0.89 (1.59) 19 C	0.68 (1.57) 19 C	0.95 (1.62) 10 C	1.00 (1.56) 6 C	0.37 (1.12) 6 B	0.26 (0.81) 3 B	0.37 (1.12) 2 B	0.37 (1.12) 2 B
p-value Trt (b)	0.595	0.842	0.020	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Baseline (b)	0.662	0.131	0.282	0.267	0.602	0.297	0.326	0.455	0.350	0.160	0.126
Root MSE (b)	1.137	1.336	1.786	1.906	1.843	1.926	1.971	1.990	2.015	2.114	2.149

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS

(b) Model: PRID = u + T(i) + B(j) + TB(ij) + error

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

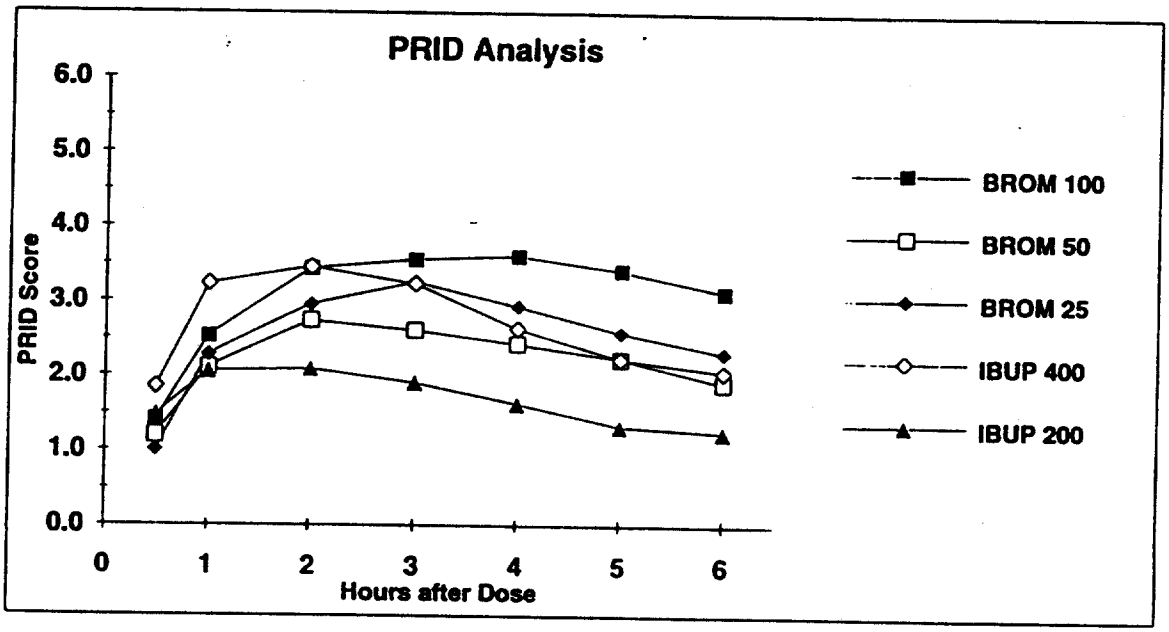
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 25 mg	31	7.15A	15.39A	4.19 A
Bromfenac 10 mg	32	5.80AB	12.63AB	3.75 A
Bromfenac 5 mg	31	5.20AB	9.19BC	3.29 AB
APAP 1000 mg	32	6.86A	12.66AB	3.75 A
Placebo	31	3.73B	5.71C	2.35 B
p-value		0.0215	0.0015	0.0070
Root MSE		4.4663	9.6182	2.0310

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)													
Treatment	1/2		1		1 1/2		2		3		4		5		6	
Bromfenac 25 mg	1.26 31 (a)	(1.37)	2.26 30	(1.73) A (d)	2.90 29	(2.12) A	3.05 26	(2.21)	3.29 26	(2.19) A	2.90 24	(2.27) A	2.48 21	(2.46) A	2.42 19	(2.46) A
Bromfenac 10 mg	1.50 32	(1.52)	1.84 32	(1.95) AB	2.56 28	(2.06) A	2.06 27	(2.26)	2.59 25	(2.31) AB	2.56 22	(2.53) A	2.00 18	(2.26) AB	1.94 16	(2.44) AB
Bromfenac 5 mg	1.35 31	(1.33)	2.35 31	(1.72) A	1.98 28	(1.81) AB	2.06 25	(2.14)	1.61 21	(1.76) BC	1.48 18	(1.84) BC	1.16 15	(1.68) BC	1.06 11	(1.79) BC
Acetaminophen 1000 mg	1.81 32	(1.64)	2.61 31	(1.94) A	2.75 28	(2.27) A	2.72 25	(2.11)	2.47 21	(2.27) AB	2.00 17	(2.41) AB	1.78 13	(2.47) AB	1.56 13	(2.38) ABC
Placebo	1.06 31	(1.36)	1.19 31	(1.42) B	1.44 25	(1.99) B	1.65 18	(2.12)	1.29 16	(2.10) C	0.61 10	(1.48) C	0.48 4	(1.43) C	0.48 4	(1.43) C
p-value Trt (b)	0.292		0.016		0.030		0.086		0.002		<0.001		0.002		0.005	
p-value Baseline (c)	0.060		0.170		0.519		0.318		0.529		0.052		0.017		0.014	
p-value Trt*Baseline (c)	0.382		0.479		0.854		0.652		0.984		0.882		0.774		0.883	
Root MSE (b)	1.438		1.761		2.061		2.169		2.143		2.125		2.074		2.108	

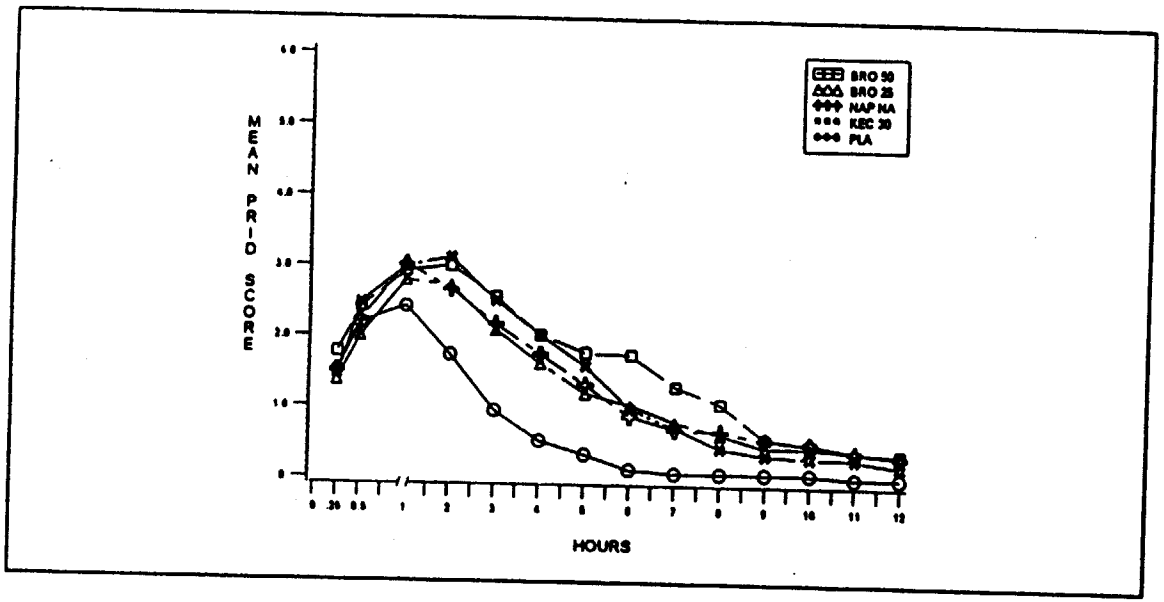
(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + error
(c) Model: PRID = u + T(i) + B(j) + TB(ij) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Bromfenac NDA 20-535
Protocol AHR-20-SW
FDA Recombined Analysis



	0.5	1	2	3	4	5	6	SPRID3	SPRID
BROM 100	1.40 (1.57) 40 NS	2.53 (1.84) 40 AB	3.43 (2.24) 39 A	3.55 (2.28) 34 A	3.60 (2.39) 32 A	3.40 (2.32) 32 A	3.13 (2.46) 29 A	8.94 (5.69) 40 A	19.06 (11.87) 40 A
BROM 50	1.20 (1.20) 40 NS	2.10 (1.52) 40 B	2.73 (2.10) 39 AB	2.60 (2.19) 28 AB	2.43 (2.22) 26 BC	2.23 (2.22) 26 BC	1.90 (2.12) 26 BC	6.98 (4.83) 40 AB	13.53 (10.55) 40 BC
BROM 25	1.00 (1.28) 40 NS	2.28 (1.47) 40 B	2.95 (1.97) 39 AB	3.25 (2.22) 34 A	2.93 (2.49) 28 AB	2.58 (2.42) 25 AB	2.30 (2.38) 24 AB	7.84 (4.94) 40 AB	15.64 (11.33) 40 AB
IBUP 400	1.85 (1.73) 40 NS	3.23 (2.22) 40 A	3.45 (2.30) 37 A	3.23 (2.48) 32 A	2.63 (2.60) 28 ABC	2.23 (2.50) 25 BC	2.05 (2.55) 20 BC	9.21 (6.02) 40 A	16.11 (12.33) 40 AB
IBUP 200	1.48 (1.69) 40 NS	2.05 (1.78) 40 B	2.08 (2.12) 35 B	1.90 (2.48) 24 B	1.63 (2.28) 21 C	1.33 (2.10) 19 C	1.25 (2.12) 16 C	5.74 (5.65) 40 B	9.94 (11.36) 40 C
p	0.132	* 0.024 *	* 0.027 *	* 0.014 *	* 0.007 *	* 0.003 *	* 0.010 *	* 0.028 *	* 0.009 *
rmse	1.51	1.79	2.15	2.33	2.40	2.32	2.33	5.44	11.50

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID [a]

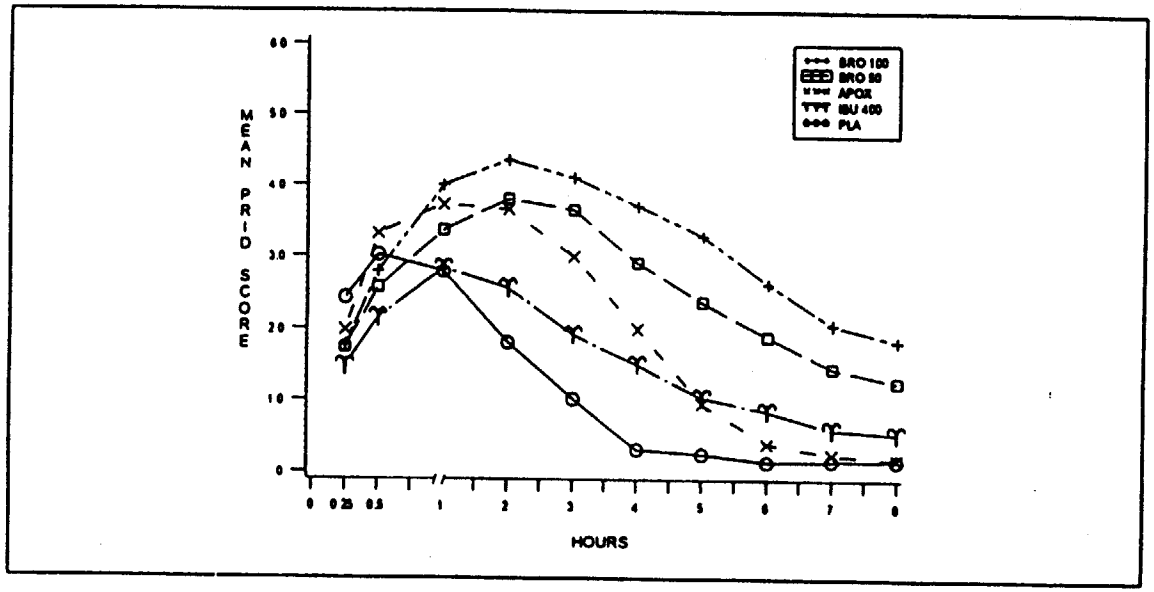
Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	41	7.83A	18.74A	3.90
Bromfenac 25 mg	43	6.95AB	14.88A	3.63
Naproxen Na 550 mg	45	7.23A	15.41A	3.89
Ketorolac 30 mg IM	42	7.91A	16.08A	3.64
Placebo	43	5.23B	7.17B	3.05
p-value		0.0494	0.0074	0.1931
Root MSE		4.6230	14.9514	1.8540

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)													
Treatment	1/4	1/2	1	2	3	4	5	6	7	8	9	10	11	12
Bromfenac 50 mg	1.78(1.42) 41 (a)	2.41 (1.69) 41	2.93(1.66) 41	3.00(2.22) 33 A (d)	2.56(2.38) 27 A	2.02(2.38) 21 A	1.78(2.44) 16 A	1.76(2.46) 14 A	1.32(2.11) 13 A	1.07(1.85) 11 A	0.59(1.50) 6	0.51(1.42) 5	0.39(1.34) 3	0.39(1.34) 3
Bromfenac 25 mg	1.37(1.41) 43	2.00(1.91) 42	2.79(1.93) 40	2.72(2.40) 30 A	2.09(2.44) 22 A	1.63(2.26) 16 A	1.21(2.08) 13 AB	1.05(2.06) 7 AB	0.81(1.74) 7 AB	0.65(1.46) 6 AB	0.47(1.35) 3	0.47(1.35) 3	0.42(1.30) 2	0.37(1.23) 2
Naproxen Na550 mg	1.51(1.41) 45	2.22(1.29) 45	3.02(1.53) 45	2.67(2.06) 36 A	2.18(2.36) 29 A	1.76(2.33) 20 A	1.33(2.15) 15 A	0.89(1.86) 11 BC	0.71(1.88) 6 AB	0.69(1.88) 5 AB	0.58(1.73) 4	0.53(1.69) 4	0.42(1.42) 3	0.36(1.37) 2
Ketorolac 30 mg IM	1.45(1.48) 42	2.48(1.71) 42	3.00(1.50) 42	3.12(2.07) 36 A	2.50(2.32) 30 A	2.02(2.19) 22 A	1.60(1.95) 20 A	1.00(1.68) 15 AB	0.74(1.62) 9 AB	0.45(1.27) 6 AB	0.36(1.19) 4	0.33(1.18) 3	0.31(1.18) 2	0.21(0.81) 2
Placebo	1.51(1.55) 43	2.19(1.84) 40	2.42(2.13) 40	1.74(2.11) 27 B	0.95(1.40) 17 B	0.53(1.30) 8 B	0.35(0.97) 6 B	0.14(0.52) 4 C	0.09(0.48) 1 B	0.09(0.48) 1 B	0.09(0.48) 1	0.09(0.48) 1	0.05(0.21) 1	0.05(0.21) 1
p-value Trt (b)	0.767	0.621	0.439	0.029	0.004	0.006	0.010	0.002	0.023	0.048	0.442	0.541	0.581	0.568
p-value Trt*Surgery (b)	0.195	0.512	0.560	0.427	0.085	0.225	0.536	0.704	0.437	0.351	0.524	0.677	0.852	0.931
p-value Trt*Baseline (c)	0.700	0.604	0.293	0.237	0.110	0.284	0.397	0.531	0.531	0.563	0.647	0.584	0.728	0.625
Root MSE (b)	1.450	1.659	1.744	2.143	2.167	2.105	1.972	1.836	1.669	1.484	1.329	1.303	1.191	1.099

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + S(k) + TS(ik) + error
(c) Model: PRID = u + T(i) + B(j) + S(k) + TB(ij) + TS (ik) + error
S = Surgery type
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 100 mg	48	10.90A	25.74A	4.75A
Bromfenac 50 mg	46	9.55A	21.03A	4.39A
APOX 650/10 mg	47	9.69A	15.40B	4.55A
Ibuprofen 400 mg	48	6.82B	12.52BC	3.48B
Placebo	47	6.15B	8.21C	3.55B
p-value		0.0001	0.0001	0.0036
Root MSE		5.4832	13.5432	2.0468

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)																	
Treatment	1/4		1/2		1		2		3		4		5		6		7		8	
Bromfenac 100 mg	1.77 48 (a)	(1.52)	2.79 48	(1.73)	4.00 48	(2.04) A (d)	4.35 42	(2.12) A	4.10 42	(2.24) A	3.71 39	(2.59) A	3.29 30	(2.79) A	2.63 25	(2.71) A	2.06 21	(2.56) A	1.83 20	(2.42) A
Bromfenac 50 mg	1.74 46	(1.81)	2.57 46	(2.27)	3.37 46	(2.48) ABC	3.80 35	(2.53) A	3.65 34	(2.52) AB	2.91 30	(2.79) AB	2.37 23	(2.79) A	1.89 20	(2.65) A	1.46 15	(2.80) A	1.26 13	(2.46) AB
APOX 650/10 mg	1.98 47	(1.59)	3.32 47	(2.13)	3.72 47	(2.25) AB	3.66 38	(2.33) A	3.00 33	(2.59) B	2.00 28	(2.46) BC	0.96 18	(2.17) B	0.40 8	(1.57) B	0.26 4	(1.45) B	0.19 2	(1.39) C
Ibuprofen 400 mg	1.47 47	(1.67)	2.15 48	(1.95)	2.83 48	(2.25) BC	2.56 34	(2.42) B	1.92 26	(2.52) C	1.50 18	(2.45) C	1.04 12	(2.26) B	0.85 8	(2.15) B	0.60 5	(1.93) B	0.54 3	(1.92) BC
Placebo	2.43 47	(1.81)	3.02 47	(1.95)	2.79 46	(1.97) C	1.81 32	(2.04) B	1.02 20	(1.91) C	0.32 10	(1.24) D	0.26 2	(1.36) B	0.15 1	(1.10) B	0.17 1	(1.17) B	0.17 1	(1.17) C
Treatment P-values (b)	0.087		0.063		0.024		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-values (c)	0.858		0.349		0.997		0.492		0.206		0.395		0.611		0.104		0.010		0.006	
Trt*Invest P-values (c)	0.221		0.675		0.237		0.526		0.665		0.693		0.640		0.775		0.581		0.513	
Root MSE (b)	1.666		1.991		2.197		2.280		2.355		2.338		2.318		2.099		1.953		1.881	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + I(k) + error
(c) Model: PRID = u + T(i) + B(j) + I(k) + TB(ij) + TI (ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Overview of Chronic (OA and RA) Studies

MEDICAL OFFICER REVIEW

NDA #: 20-535
NAME: Bromfenac Sodium.
SPONSOR: Wyeth-Ayerst
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: December 19, 1995.
CSO: C. Koerner

INTRODUCTION:

In the NDA the sponsor submitted reports of three complete osteoarthritis (OA) and two complete rheumatoid arthritis (RA) studies. At the time of submission, the sponsor was seeking an OA indication but not an RA indication. The request for an OA indication was withdrawn after the filing meeting, when it was called to the sponsor's attention that the quantity and duration of the safety data was inadequate to support an OA indication. Thus, the studies discussed here are not pivotal for efficacy. However, they do provide the only source of chronic safety data. These brief reports are presented here as background information.

Study Number	Disease	Total N	Design	Controls
18	OA	144	6 week	Aspirin, placebo
303	OA	394	6 week 1 year OL ext.	Naproxen, placebo
309	OA	333	4 week DB with placebo 1 year DB ext. OL ext.	Ibuprofen, placebo
23	RA	18	8 week	(none)
305	RA	385	36 week	Diclofenac

DB=double-blind, OL=open-label

OSTEOARTHRITIS STUDIES:

OA Study 18

This was a 6-week, randomized, double-blind, parallel, active- and placebo-controlled study of bromfenac, aspirin and placebo in OA patients. It was conducted in 6 sites in the U.S. and Canada. The total sample size was 144, were treatments assigned as follows:

N	Drug	Regimen	Daily Dose
26	Bromfenac	25 mg qid	100 mg/d
26	Bromfenac	10 mg qid	40 mg/d
22	Bromfenac	5 mg qid	20 mg/d
22	Aspirin	1000 mg qid	4000 mg/d
22	Aspirin	650 mg qid	2600 mg/d
24	Placebo		

Patients were instructed to take the study medication with food.

The primary variables were patient and physician globals and weigh-bearing pain. Efficacy assessments were done at 1, 2, 4 and 6 weeks.

The 25 and 10 mg doses surpassed placebo for all three primary endpoints at all times. The two dosed performed similarly and were usually numerically at least as good as aspirin 650 mg.

The only serious adverse event was a myocardial infarction. There were two discontinuations for elevated liver enzymes, one in the bromfenac 5 mg group and one in the aspirin 1000 mg group.

OA Study 303

This was a 6-week randomized, double-blind, parallel, active and placebo-controlled study of bromfenac, naproxen and placebo in OA patients. There was an optional open-label follow-up on bromfenac for one year. It was conducted at 15 sites. The total sample was 395 patients, but 1 had no post-baseline data. The remaining 394 were assigned treatment as follows:

N	Drug	Regimen	Daily Dose
77	Bromfenac	50 mg bid	100 mg/d
79	Bromfenac	25 mg qid	100 mg/d
78	Bromfenac	25 mg bid	50 mg/d
83	Naproxen	500 mg bid	1000 mg/d
77	Placebo		

Patients were instructed to take the study drug at least 1 hour before meals or at least 2 hours after meals. In the open-label extension dosing started at bromfenac 50 mg bid, but could be adjusted to 25 mg qid, tid or bid. There were 334 patients providing data from the extension; the predominant dose was 100 mg/day.

Efficacy was assessed at 1, 2, 4 and 6 weeks. Primary endpoints were patient and physician globals, walking pain and tenderness on palpation. Population PK sample were also taken as part of this study.

All active treatments were better than placebo at all weeks for both globals and walking pain. They all also were better than placebo for nighttime pain and inactivity stiffness.

There was one ulcer with naproxen and one with bromfenac 25 mg bid. Two patients taking bromfenac had elevations of SGPT over 8 time upper limit of normal at 42 ad 43 days (vol. 1.208 p. 124). There were 14 patients (4%) discontinued for liver enzyme elevations; the earliest was at 37 days. Patients over age 65 had the same dropout rate, but tended to dropout move to adverse events than lack of efficacy. The opposite was true for those under 65.

OA Study 309

This was a 4-week randomized, double-blind, parallel, active- and placebo-controlled trial of bromfenac, ibuprofen and placebo. This was followed by a 1-year double blind extension in which placebo patents from the first segment were re-randomized to bromfenac or ibuprofen. An open-label extension was added later. After washout up to 2 weeks patients were assigned treatments for the first 4 weeks as follows (of 333 who entered, 332 received medication):

N	Drug	Regimen	Daily Dose
108	Bromfenac	50 mg tid	150 mg/d
112	Ibuprofen	600 mg tid	1800 mg/d
112	Placebo		

Patients were instructed to take the study medication at least 1 hour before meals, but were allowed to take it closer to meals if they had problems taking it as instructed. After the four weeks patients could enter a double-blind, 52-week extension. Placebo patients were re-randomized, so that 151 patients entered the double-blind extension taking bromfenac, 152 entered taking naproxen. Titration was allowed within the range 75 to 225 mg/day for bromfenac and 900 to 2700 mg/day for ibuprofen. After 16 weeks on the extension dose was to be held steady, but could be reduced if it was not tolerated.

Primary endpoints were patient and physician globals and walking pain. Efficacy assessments were done at 1, 2, and 4 weeks. PK samples were also collected.

In segment 1, bromfenac was superior to placebo and ibuprofen for all three endpoints at all timepoints. Ibuprofen was not consistently superior to

placebo. It turned out that 85% of patients took bromfenac less than 1 hour before meals.

The bromfenac group had more reports of dyspepsia, nausea, elevated alkaline phosphatase, and elevated SGOT than ibuprofen. The ibuprofen group had more reports of hypokalemia and edema. Four bromfenac patients was PUB events, 5 were discontinued due to liver enzyme elevation, 11 had liver enzymes of 3 to 8 x ULN, and 1 had liver enzymes > 8 x ULN. Three ibuprofen patients had PUB events, 3 were discontinued due to liver enzyme elevations, 2 had liver enzymes of 3 to 8 x ULN, and 1 had liver enzymes > 8 x ULN. The predominant bromfenac dose was 200 mg/day or more for 26% of patients and 150 mg/day or less for 50% of patients.

RHEUMATOID ARTHRITIS STUDIES:

RA Study 23

This was an 8-week randomized, double-blind, parallel, uncontrolled dose-response tolerability study of bromfenac in RA patients. It was conducted at a single site.

The total sample size was 18, treatments were assigned as follows:

N	Drug	Regimen	Daily Dose
6	Bromfenac	50 mg qid	200 mg/d
6	Bromfenac	25 mg qid	100 mg/d
6	Bromfenac	10 mg qid	40 mg/d

Patients were told to take the study medication with food.

There was no statistical efficacy analysis because of the study's small size. The 50 mg dose seemed to have an effect, and the 10 mg dose looked better than the 25 mg dose.

One patient was withdrawn after 15 days for abdominal pain and eructation. She also had mildly increased BUN and creatinine. Four patients had some elevation of liver enzymes; but 3 had it present at baseline. One patient had a new elevation to SGPT, to 1.15 x ULN, by 8 weeks.

RA Study 305

This was a 36-week randomized, double-blind, parallel, active-controlled study of bromfenac and diclofenac in RA patients. It was conducted at 15 sites. The total sample was 385 patients, but 1 had no post-baseline data. The remaining 384 were assigned treatment as follows:

N	Drug	Regimen	Daily Dose
76	Bromfenac	100 mg bid	200 mg/d
78	Bromfenac	50 mg qid	200 mg/d
75	Bromfenac	50 mg bid	100 mg/d
77	Bromfenac	25 mg qid	100 mg/d
78	Diclofenac	75 mg bid	150 mg/d

Patients were instructed to take the drug at least 1 hour before meals or at least 2 hours after meals.

The primary endpoints were patient and physician globals, swollen joints, and painful joints. There was improvement from baseline, but differences between treatments were sporadic. At weeks 1 through 4 6 to 16% of patients took medication with meals; it did not appear to effect the globals or swollen joints.

The 100 mg bid dose had more adverse events and more discontinuations for adverse events than the 50 mg qid dose (same daily dose). The 100 mg bid dose did have the second lowest rate for lack of efficacy discontinuations.

There were 9 bromfenac patients who discontinued with elevated liver enzymes. Seven received the 100 mg bid dose. The two earliest discontinuations were at 21 and 35 days. One patient receiving 50 mg qid discontinued at 19 days with liver enzyme elevations as a secondary reason. One patient taking 25 mg qid discontinued for enzyme elevations at 169 days.

CONCLUSIONS:
Neither the OA or RA indications could be supported because of the lack of sufficient long-term safety data. The RA studies would not provide substantial evidence, but it appears that the OA studies would be able to provide evidence of efficacy.

It is worth noting that bromfenac appeared to be effective even when taken with food, as in OA Study 18, or when most patients took it within an hour before meals, as in OA Study 309.

In RA Study 305, where the 200 mg/day dose was given as bid or qid dosing, the principal difference was than bid dosing tended to be associated with more adverse events.

Evidence of hepatotoxicity was seen in these studies, notably in OA Study 303, OA Study 309 and RA Study 305.

RECOMMENDATIONS:
Since the OA and RA indications are not being sought, no specific efficacy or treatment recommendations come from these studies. The safety data from these studies, however, are pertinent to the safety evaluation for this application, and are reviewed elsewhere in the NDA Review Pack.

The OA studies will require a more critical review if the sponsor later seeks an OA indication using these studies.

John E. Hyde
John E. Hyde, Ph.D., M.D

Rm. W Duncan 1-5-98

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MEDICAL OFFICER REVIEW

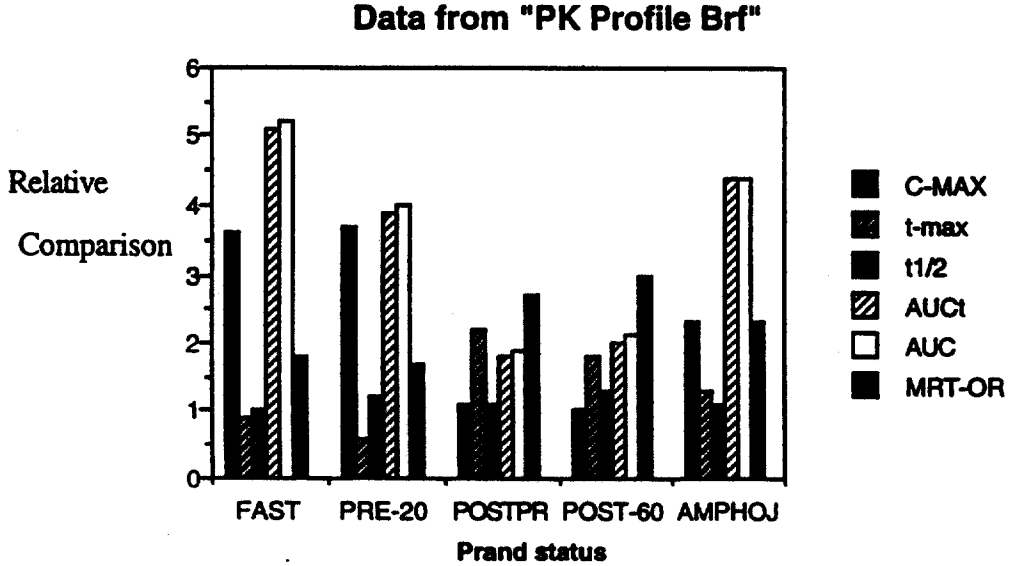
NDA# : 20-535 Protocol 's 792-A-304-US and 792-A-307-US.

TITLE: A Multiple- Dose Comparison of Bromfenac 50 mg, 25 mg, and 10 mg, Anaprox sodium 550/275 mg, Ibuprofen 400 mg, and Placebo, for the Treatment of Dysmennorhea.

Drug: Bromfenac (sodium [2- amino-3-(p-bromobenzoyl)-phenyl] acetate sesquihydrate.

ABSTRACT

BACKGROUND: Bromfenac sodium (AHR-1028-B) is a non-steroidal anti-inflammatory drug (NSAID) possessing non-narcotic analgesia properties. Bromfenac is one of a series of 2-amino-3-benzoylphenylacetic acid derivatives. According to the sponsor, Bromfenac has been shown to be well tolerated and well absorbed in healthy men and women after oral doses administered before meals. Single doses as high as 200 mg were administered in a safety study, and doses as high as 100 mg q.i.d. were administered in a 28 day double blind, placebo-controlled safety and tolerance study. The bioavailability of 50-mg single oral doses was significantly reduced when the drug was administered with food.See Bar Graph below.



According to the sponsor, the results of single-dose, double-blind, placebo-controlled clinical trials with post-surgical pain models suggested that Bromfenac in doses of 10, 25, and 50 mg were as effective as Ibuprofen 400 mg, aspirin 650 mg, and acetaminophen 1000 mg following oral or orthopedic surgery. Higher doses of Bromfenac (50-100 mg) were generally associated with longer duration of action without further increases in peak

analgesia activity. Once again, according to the sponsor, Bromfenac has been shown to be effective in the treatment of dysmenorrhea. The results of double-blind, placebo-controlled four-period crossover studies suggested that Bromfenac in single and multiple oral doses of 50 mg , 25 mg, and 10 mg were at least as effective as Naproxen sodium and Ibuprofen in the usual therapeutic doses.

The IND for Bromfenac was originally submitted to the FDA by A.H. Robins in JULY 1984. American Home Products, after buying A.H. Robins, transferred the IND to Wyeth - Ayerst Laboratories in May 1990.

THE MATERIAL FOR REVIEW:

The submission consists of the final study reports for NDA # 20 - 535 -Protocol #'s 792-A-304 US and 92-A-307-US. The two studies were designed by the sponsor to show the relative efficacy and safety of Bromfenac 10, 25, and 50 mg Vs Anaprox 550/275 mg and Ibuprofen 400 mg in the treatment of dysmenorrhea. The Protocol # AHR-06-US (1986-89) had been investigated at the cite and fell short of the necessary requirements to be considered as a pivotal study. Recently (October 16, 1995), DSI had investigated the site where 792-A-307 US was accomplished and there were some serious questions that were answered on November 17, 1995 (DSI stated that this study will not be incorperated in this NDA because of lost documentation and serious violations in the carring out of the clinical trials.This has left only one study to be evaluated for dysmennorrhea.

Study # 792-A-304-US : This was a single-center , double-blind, four-period crossover, placebo-controlled outpatient study conducted to compare the efficacy and safety of Bromfenac 50 mg and 10 mg and Naproxen sodium 550 mg / 275 mg for the relief of primary dysmenorrhea. Both were compared to placebo. The study was conducted by Robert Fulmer M.D. in the U.S.A. . Fifty-four (54) women ingested the study medication at least once for one cycle of the study and had data available for safety analysis. They were 18 to 45 years of age (mean 32.2 years) and weighed from 46 to 119 kg (mean 67.5 kg). Fifty one(51) patients had data available for intent-to-treat efficacy analysis. Presently there are some questions concerning safety of Bromfenac and whether there is adequate information to make an informed analysis. DSI 's report 11/6-7/95 will be evaluated and incorporated into this report.

EFFICACY ANALYSIS :As seen by the pain relief (PAR) graph below, both Bromfenac 50 mg and 10 mg were better than Placebo. Bromfenac 10 mg was slightly better than 50 mg and Anaaprox sodium was slightly better than Bromfenac 50 mg.

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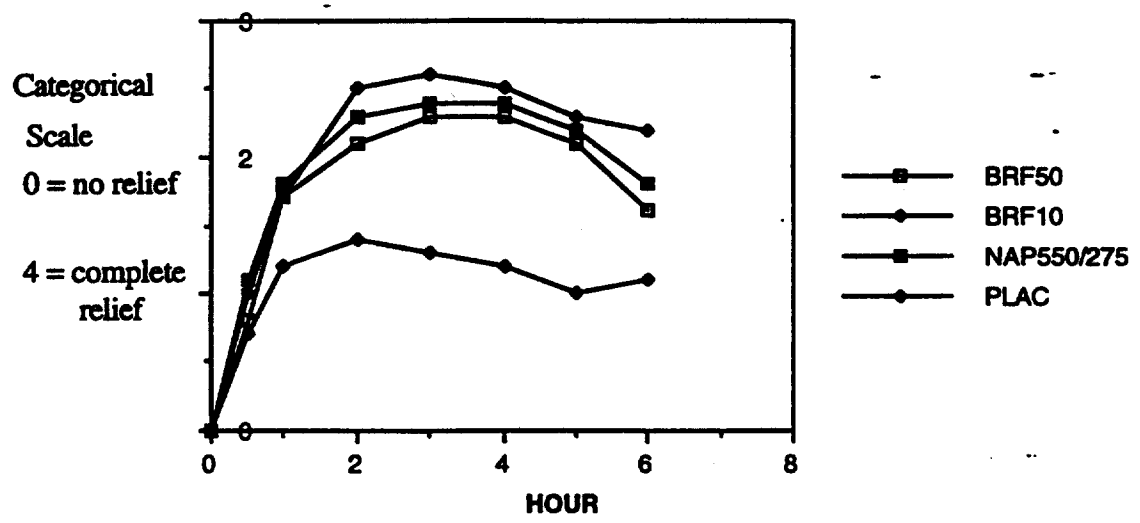
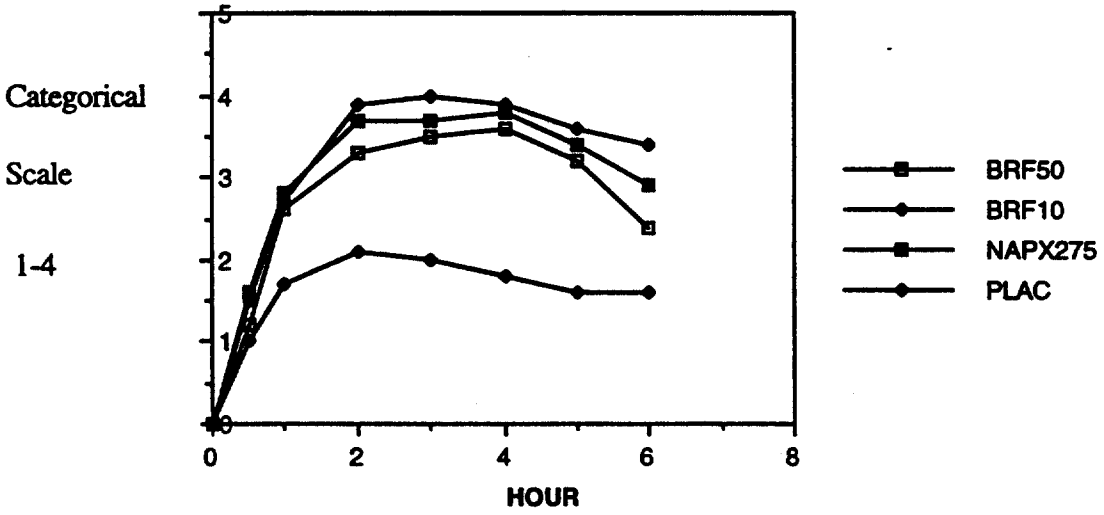
Mean Pain Relief Scores GRAPH I



Pain Relief Intensity Difference (PRID) is graphically demonstrated in GRAPH II. Once again, both Bromfenac 50 and 10 mg were better than placebo. Bromfenac 10 mg was slightly better than Bromfenac 50 mg and Anaprox sodium 275 mg. Anaprox sodium was somewhat better than Bromfenac 50 mg.

GRAPH II PRID



SAFETY ANALYSIS: I. Protocol # 792-A-304: one or more study events were reported for 23 patients (44%) who received bromfenac 50 mg, 17 % (33%) who received bromfenac 10 mg, 24 (45%) who received Naproxen sodium, and 22 (43%) who received placebo. There were two statistically significant differences for specific study events (dyspepsia and sinusitis, the same reeported for TESE).

CONCLUSION :(1) It appears from the data presented above that Bromfenac 10 mg is the most effective of the Bromfenac doses. Further explanation of this phenomenon is needed.

(2) Since the Sponsor is planning on packageing 50 and 25 mg capsules a Dysmennorrhea study using these doses would be adviseable.

(3) Bromfenac 10 mg , 25 mg and 50 mg were better than Placebo.

DR B. KOPP M.D.

CONFIDENTIAL: SBA Summary for Bromfenac Protocol AHR-06-US

A Multiple-dose Comparison of Bromfenac Sodium (AHR-10282B) 25 mg and 5 mg and Placebo in Fasted and Fed Patients With Primary Dysmenorrhea.

IND DRUG:	Bromfenac	DOSES:	25, 5 mg oral
REFERENCE DRUGS:	Placebo		
TOTAL PTS ENROLLED:	143	DURATION OF DOSING:	Single dose, 6 hr Multiple dose, up to 3 days
INVESTIGATOR:	Multicenter		

PURPOSE: This study was designed to assess the analgesic activity and safety of bromfenac, 25 mg and 5 mg, and placebo, self-administered with or without food, in the treatment of patients with primary dysmenorrhea.

METHOD: This phase II, three-period crossover, randomized, double-blind study was conducted at eight sites (one additional investigator received study medication but did not enroll any patients). The patients were randomly assigned to take one capsule of study medication either with or without food when the pain of dysmenorrhea was moderate to severe in intensity. Additional doses, at least 4 hours apart, could be taken up to six times a day. A maximum of 16 doses could be taken in any single menstrual period. Patients were permitted to take rescue medication if two successive doses of study medication were not sufficient; no efficacy data were collected thereafter.

The primary variables were sum of pain analog intensity differences (SPAID, 3 and 6 hours), and peak pain analog intensity difference (peak PAID). Other variables were considered secondary for evaluation of efficacy (hourly PAIDs, dose 1, day 1 and day 2 pain-relief assessments, global assessments and dur-PRs). Onset of pain relief (on-PR) was not computed for this study because categorical pain relief and pain intensity scores were not collected.

RESULTS: One hundred forty-three (143) women took study medication for at least one cycle. Their ages ranged from 18 to 50 years (mean, 31.5 years) and their weight range was 42.6 to 113.4 kg (mean, 66.1 kg). One hundred and thirty-eight patients (138) had some data for all 3 cycles for the intent-to-treat efficacy analysis.

Primary variables: For the combined fasted and fed subgroups ("all patients"), both bromfenac doses were significantly superior to placebo for all primary efficacy variables. In both the fasted and fed subgroups, bromfenac 25 mg was superior to placebo for 3-hour and 6-hour SPAID, and peak PAID scores. Bromfenac 5 mg (fasted and fed) was consistently superior to placebo (fasted), but bromfenac 5 mg (fed) was not distinguishable from placebo (fed). The differences in the mean values between the fasted and fed subgroups for either bromfenac dose were not statistically significant; the fed patients had consistently higher efficacy scores.

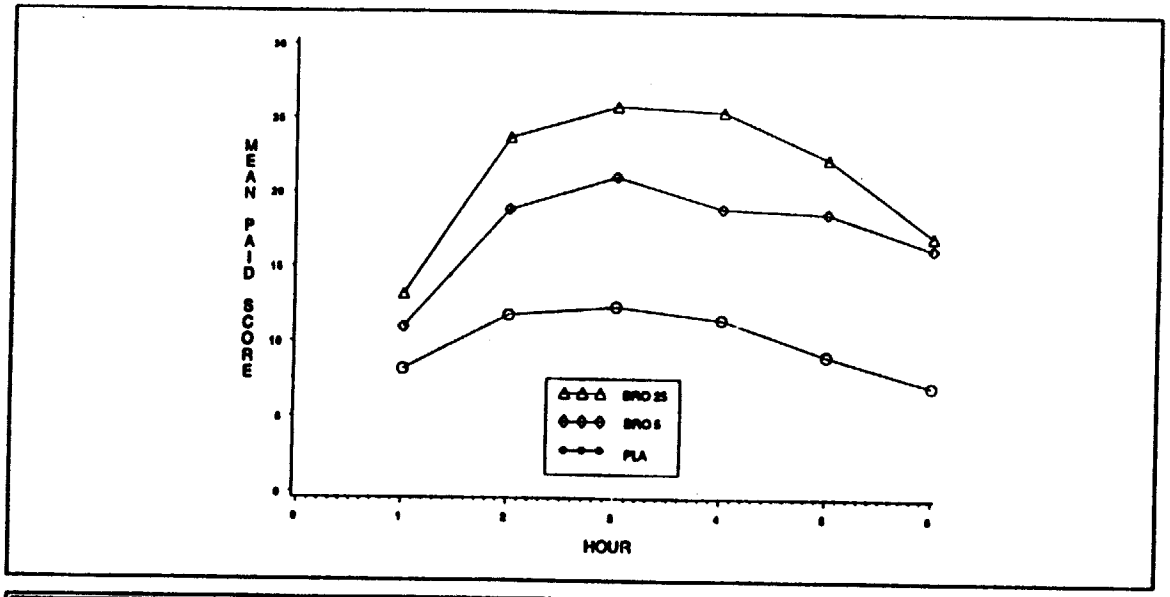
Secondary variables: For all patients (fasted and fed), bromfenac 25 mg was superior to bromfenac 5 mg and placebo for dose 1, day 1 and day 2 pain-relief and global assessments. Bromfenac 5 mg was superior to placebo for dose 1 and day 1 pain-relief and global assessments for all patients. In both the fasted and fed subgroups, bromfenac 25 mg and 5 mg were superior to placebo for dose 1 pain-relief assessments. Bromfenac 25 mg taken under both fasted and fed conditions was superior to bromfenac 5 mg (fed) and placebo in day 1 pain-relief and global assessments. The pain relief scores for dose 1, day 1 and day 2 and the global assessments showed no significant differences between the fasted and fed subgroups within the same treatment group.

One hundred forty-three (143) patients had data available for the safety analysis. Among all patients (fasted and fed), one or more study events were reported by 14 patients taking bromfenac 25 mg, by 23 patients taking bromfenac 5 mg and by 16 patients taking placebo. One patient (placebo-treated) withdrew for nausea and vomiting. No serious study events or potentially clinically significant laboratory results were reported.

CONCLUSIONS: Bromfenac 25 mg whether taken under fasted or fed conditions was consistently statistically superior to placebo for all primary variables. Bromfenac 5 mg (fasted and fed) was superior to placebo (fasted) but bromfenac 5 mg (fed) was not different from placebo (fed), due to a higher response in the placebo fed subgroup than the placebo fasted subgroup. Numerical differences between the bromfenac food subgroups were small and the effect of food on the mean analgesic response was clinically negligible. The tolerance of all treatments was comparable and acceptable.

Figure 1, Table 1. Mean Scores of Pain Analog Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPAID AND PEAK PAID

Treatment Group	n	3-hour SPAID	Final SPAID	Peak PAID
Bromfenac 25 mg	132	49.71 A	118.94 A	33.92 A
Bromfenac 5 mg	132	40.22 A	96.36 A	29.55 A
Placebo	132	26.04 B	56.30 B	21.29 B
p-value Trt		0.0001	0.0001	0.0001
Trt*Period p-value		0.5285	0.9533	0.9186
Trt*Investigator p-value		0.1548	0.3817	0.3216
Root MSE		45.21	102.26	21.52

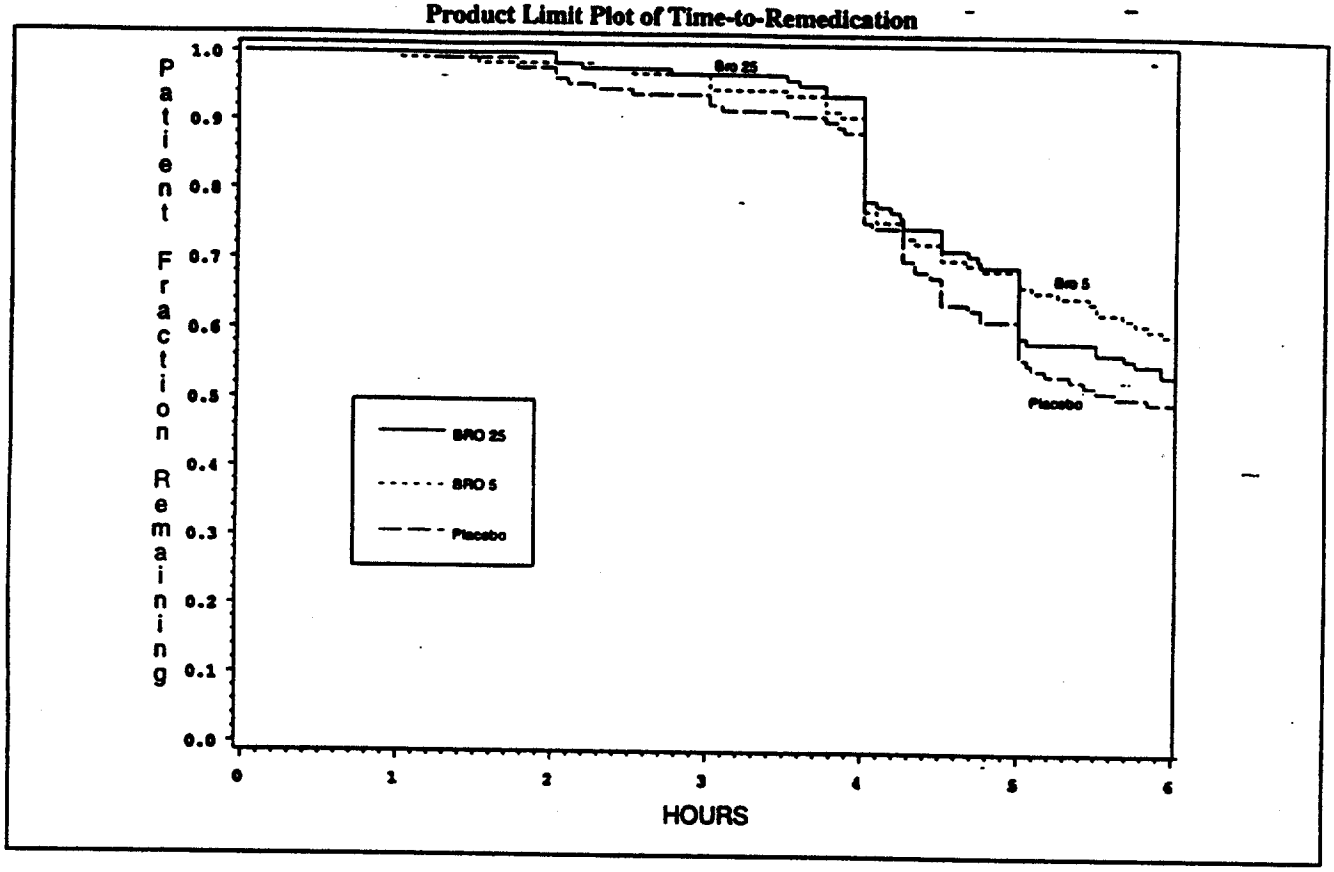
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours) 1		2		3		4		5		6	
Bromfenac 25 mg	13.13 131 (a)	(16.26) A (c)	23.68 130	(22.60) A	25.82 126	(24.91) A	25.46 122	(24.95) A	22.30 89	(25.26) A	17.10 68	(25.08) A
Bromfenac 5 mg	10.91 132	(20.41) AB	18.79 130	(26.36) A	21.05 128	(28.02) A	18.91 118	(28.44) A	18.58 90	(25.95) A	16.24 78	(25.45) A
Placebo	8.14 131	(17.53) B	11.73 128	(24.24) B	12.33 124	(26.86) B	11.47 114	(24.84) B	9.08 78	(21.02) B	7.11 63	(20.75) B
Overall Treatment p-value (b)	0.0073		0.0001		0.0001		0.0001		0.0001		0.0001	
Treatment*period p-value (b)	0.1568		0.5777		0.9766		0.7717		0.9974		0.8643	
Treatment*investigator p-value (b)	0.2218		0.2231		0.2410		0.5960		0.9136		0.7146	
Root MSE (b)	16.57		21.13		23.54		23.55		22.73		21.92	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS
F: Food = Fed/Fasted, P: Period.

(b) Model: PAID = u + B + T(i) + P(j) + I(k) +F(l) + TP(ij) + TI(ik) + TF(il) + Pat(I(k)*F(l)) + error

Figure 2. Estimated Duration of Analgesia



(Time-to-Remedication)

Table 2. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 25 mg	132	5:12 [c]	(5:02, 5:21)
Bromfenac 5 mg	132	5:12	(5:01, 5:23)
Placebo	132	4:57	(4:45, 5:09)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied. No significant difference.

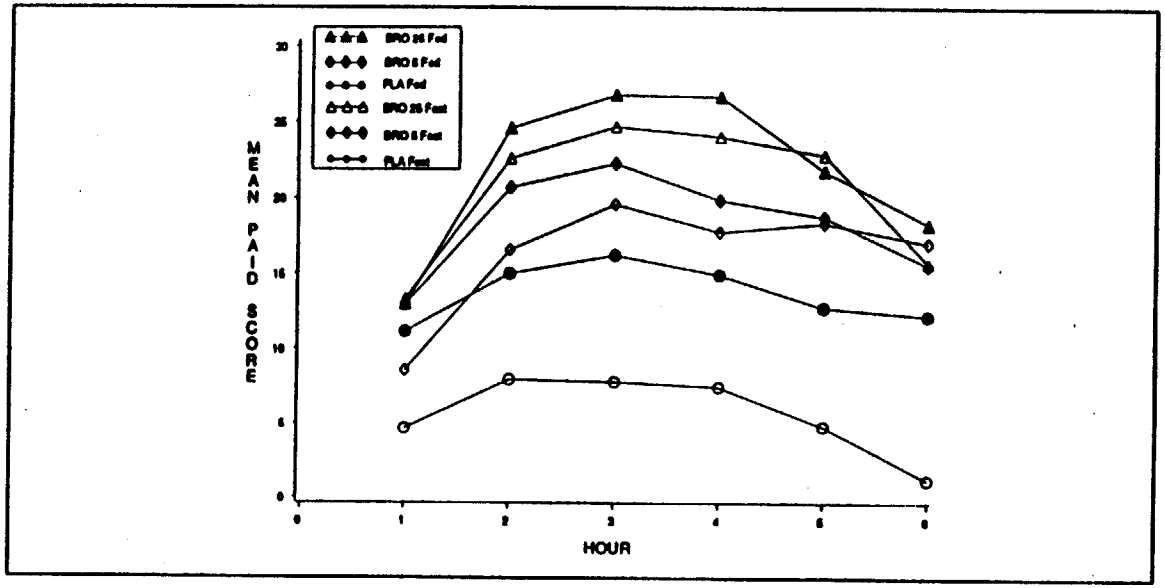
Table 3. Time-to-Remedication (Percentiles)

Treatment	Percentiles In Hours:minutes (95% C. I.)		
	25%	50% (Median)	75%
Bromfenac 25 mg	4:15 (4:00, 5:00)	>6h (5:03, >6h)	>6h (NE)
Bromfenac 5 mg	4:15 (4:00, 5:00)	>6h (NE)	>6h (NE)
Placebo	4:12 (4:00, 4:30)	5:50 (5:00, >6h)	>6h (NE)

NE: Not estimable.

Figure 3, Table 4. Mean Scores of Pain Analog Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPAID AND PEAK PAID

Treatment Group	n	3-hour SPAID	Final SPAID	Peak PAID
Fasted, Bromfenac 25 mg	61	48.30 A	115.43A	34.18 A
Fed, Bromfenac 25 mg	71	50.94A	121.95A	33.69A
Fasted, Bromfenac 5 mg	61	34.90AC	89.35A	29.56A
Fed, Bromfenac 5 mg	71	44.80AC	102.38AC	29.54AC
Fasted, Placebo	61	16.48B	33.21B	15.70B
Fed, Placebo	71	34.25BC	76.14BC	26.08C
Overall Treatment p-value		0.0001	0.0001	0.0001
Overall Food p-value		0.1223	0.1369	0.3048
Treatment*food p-value		0.3473	0.2480	0.0599
Root MSE		45.21	102.26	21.52

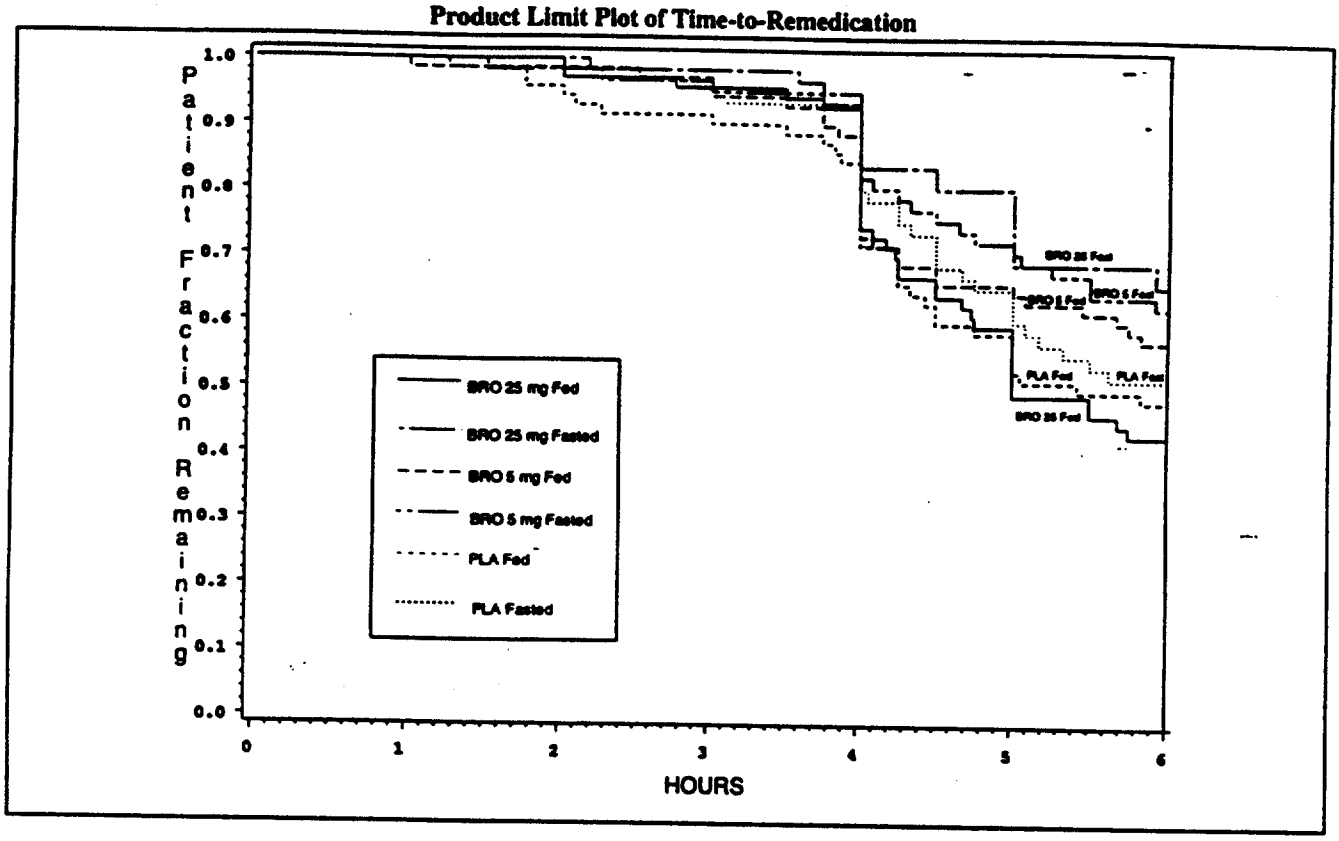
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

Treatment	Assessment Time Points (Hours)											
	1		2		3		4		5		6	
Fasted, Bromfenac 25 mg	13.33 60 (a)	(17.70) A (c)	22.62 60	(23.86) A	24.70 60	(25.97) A	24.07 58	(24.55) A	22.85 49	(25.84) A	15.70 40	(25.64) A
Fed, Bromfenac 25 mg	12.96 71	(15.04) A	24.59 70	(21.60) A	26.77 66	(24.11) A	26.66 64	(25.41) A	21.82 40	(24.93) A	18.30 28	(24.71) A
Fasted, Bromfenac 5 mg	8.54 61	(21.81) AB	16.56 60	(27.43) AC	19.61 59	(30.22) A	17.77 57	(29.61) AC	18.36 44	(27.52) A	17.03 38	(28.95) A
Fed, Bromfenac 5 mg	12.94 71	(19.05) A	20.70 70	(25.44) AD	22.30 69	(26.14) A	19.88 61	(27.57) AD	18.77 46	(24.72) AC	15.56 40	(22.20) AC
Fasted, Placebo	4.66 61	(12.56) B	7.93 61	(22.66) B	7.79 59	(26.33) B	7.44 56	(21.87) B	4.80 39	(18.12) B	1.18 30	(15.28) B
Fed, Placebo	11.13 70	(20.49) AB	15.00 67	(25.22) BCD	16.24 65	(26.88) B	14.93 58	(26.81) BCD	12.75 39	(22.72) BC	12.20 33	(23.42) C
Overall Treatment p-value (b)	0.0073		0.0001		0.0001		0.0001		0.0001		0.0001	
Overall Food p-value (b)	0.1289		0.1628		0.1955		0.1523		0.4839		0.1121	
Treatment*food p-value (b)	0.2064		0.5319		0.4193		0.5659		0.1977		0.0395	
Root MSE (b)	16.57		21.13		23.54		23.55		22.73		21.92	

(a) Sample sizes, not extrapolated
(c) Fisher's Protected LSD based on Model (b) LSMEANS
F: Food = Fed/Fasted, P: Period.

(b) Model: PAID = u + B + T(i) + P(j) + I(k) +F(l) + TP(ij) + TI(ik) + TF(il) + Pat(I(k)*F(l)) + error

Figure 4. Estimated Duration of Analgesia



(Time-to-Remedication)

Table 5. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Fasted, Bromfenac 25 mg	61	5:25[c]	(5:12 - 5:38)
Fed, Bromfenac 25 mg	71	4:55	(4:41 - 5:09)
Fasted, Bromfenac 5 mg	61	5:17	(5:01 - 5:33)
Fed, Bromfenac 5 mg	71	5:05	(4:50 - 5:20)
Fasted, Placebo	61	4:58	(4:45 - 5:11)
Fed, Placebo	71	4:51	(4:34 - 5:08)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied. No significant difference.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Fasted, Bromfenac 25 mg	5:00 (4:00, >6h)	>6h (NE)	>6h (NE)
Fed, Bromfenac 25 mg	4:00 (4:00, 4:40)	5 (4:44, >6h)	>6h (NE)
Fasted, Bromfenac 5 mg	4:39 (4:00, 5:55)	>6h (NE)	>6h (NE)
Fed, Bromfenac 5 mg	4:00 (4:00, 5:05)	>6h (5:40, >6h)	>6h (NE)
Fasted, Placebo	4:20 (4:00, 5:00)	>6h (5:00, >6h)	>6h (NE)
Fed, Placebo	4:00 (4:00, 4:26)	5:25 (4:30, >6h)	>6h (NE)

NE: Not estimable.

Appendix I

CONFIDENTIAL: SBA Summary for Bromfenac Protocol 792-A-304-US

A Multiple-dose Comparison of Bromfenac (AHR 10282B) 50 and 10 mg, Naproxen Sodium (Anaprox®) 550/275 mg and Placebo for the Treatment of Dysmenorrhea.

IND DRUG:	Bromfenac	DOSES:	50, 10 mg oral
REFERENCE DRUGS:	Naproxen sodium Placebo	DOSE:	550/275 mg oral
TOTAL PTS ENROLLED:	54	DURATION OF DOSING:	Single dose, 6 hr Multiple dose, up to 3 days
INVESTIGATOR:	Robert Fulmer, M.D., Austin, TX, United States		

PURPOSE: The present study was designed to demonstrate 1) the analgesic activity of bromfenac at single and multiple oral doses of 10 mg and 50 mg, and 2) to compare the analgesic efficacy of single and multiple doses of these bromfenac regimens to that of naproxen sodium 550 mg (loading dose) followed by 275 mg in patients experiencing moderate or severe pain of primary dysmenorrhea, and 3) to assess the safety of these treatments in patients with primary dysmenorrhea.

METHOD: This was a single-center, double-blind, four-period crossover, placebo-controlled outpatient study comparing the efficacy and safety of bromfenac and naproxen sodium for the relief of primary dysmenorrhea. Four treatment regimens of bromfenac 50 mg, bromfenac 10 mg, naproxen sodium 550 mg (loading dose) followed by 275 mg doses, and placebo were randomly assigned to women over the course of four menstrual cycles. Patients were instructed to take the first dose of study medication when the pain of dysmenorrhea was considered to be at least of moderate intensity. A repeat dose could be taken after at least four hours. Patients recorded their pain intensity and pain relief for 6 hours after the first dose and additional efficacy assessments were done on the second day.

The primary efficacy variables were total pain relief (TOPAR, 6 hours), sum of pain intensity differences (SPID, 6 hours), and sum of pain relief and pain intensity difference (SPRID, 6 hours). These variables were calculated from the area under the pain relief-, PID (pain intensity difference)-, and PRID (pain relief plus PID scores)- time curves, respectively by using the trapezoidal rule. Other variables were considered secondary for evaluation of efficacy (timed pain relief, PID, and PRID scores, global assessments and preference rating, on-PR and dur-PR).

RESULTS: Fifty-four (54) women ingested the study medication at least once for one cycle of the study and had data available for safety analyses. They were 18 to 45 years of age (mean 32.2 years) and weighed from 46 to 119 kg (mean, 67.5 kg). Fifty one (51) patients had data available for all 4 treatments and were used in the intent-to-treat efficacy analyses. For all primary variables, both bromfenac doses and naproxen sodium were significantly superior to placebo (<0.001). Both doses of bromfenac (50 and 10 mg) and naproxen sodium were superior to placebo for dose 1 global assessment and preference rating.

One or more treatment-emergent study events were reported during the active treatment interval by 13 patients (25%) who received bromfenac 50 mg, 15 (29%) patients who received bromfenac 10 mg, 20 (38%) patients who received naproxen sodium, and 19 (37%) patients who received placebo. There were no serious or unexpected adverse effects. No patients withdrew from the study because of an adverse effect.

CONCLUSIONS: The results of this study indicate that single and multiple oral doses of 50 mg and 10 mg of bromfenac are at least as effective as the usual therapeutic doses of naproxen sodium in providing relief from pain due to dysmenorrhea. The tolerance of all treatments was acceptable.

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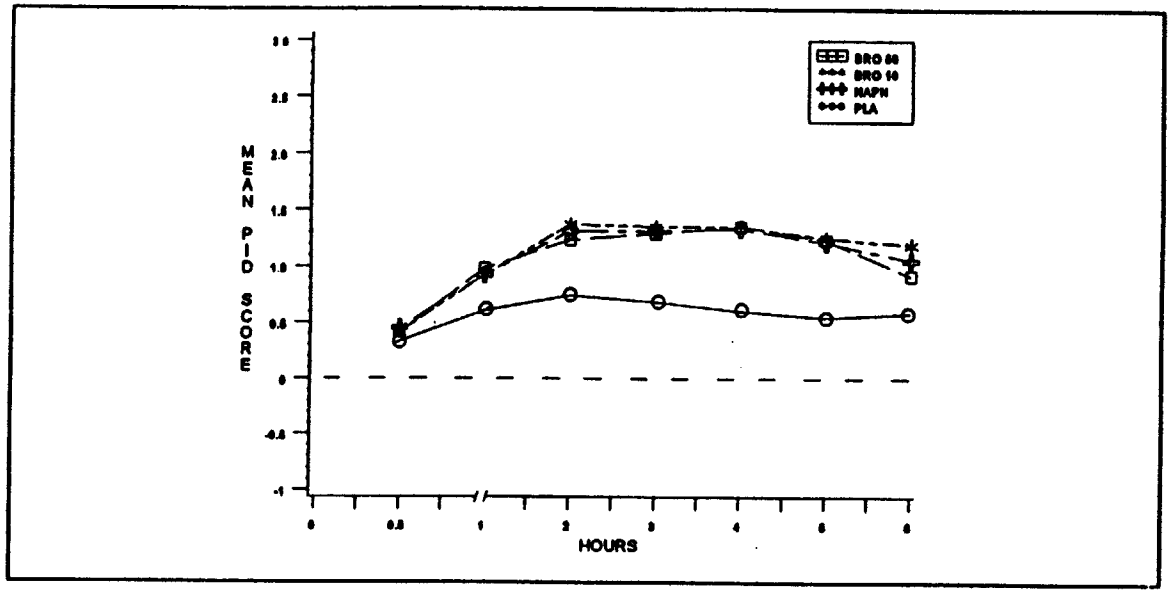
Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID[a]

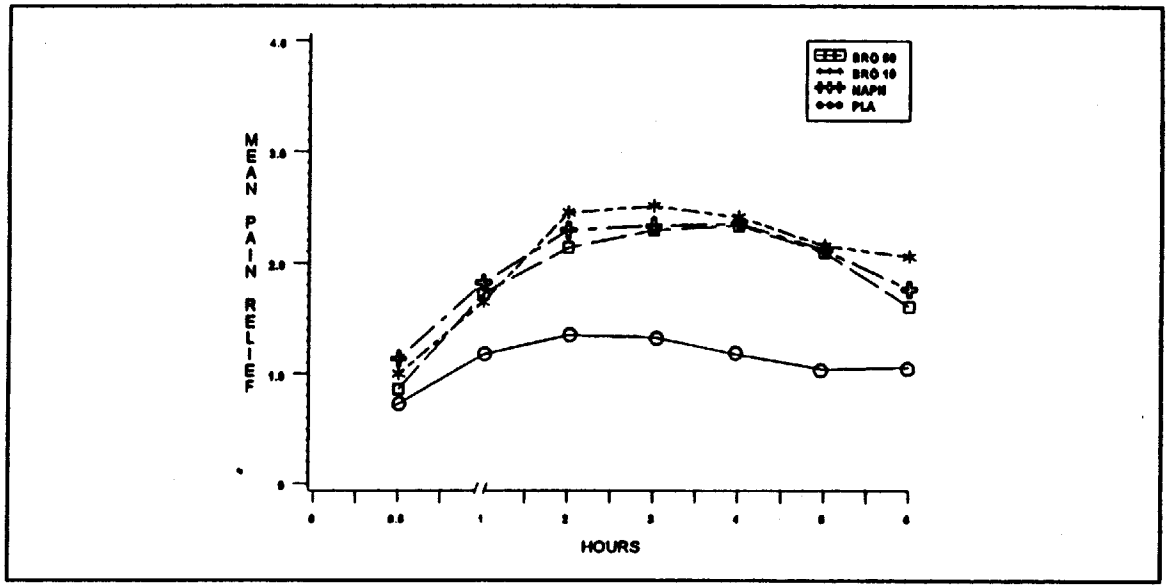
Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	51	2.82A	6.52A	1.55A
Bromfenac 10 mg	51	2.95A	6.83A	1.67A
Naproxen Na 550 mg	51	2.89A	6.62A	1.67A
Placebo	51	1.71B	3.50B	1.12B
p-value Trt		0.0002	0.0001	0.0001
p-value Trt*Period		0.3097	0.2945	0.2579
Root MSE		1.7393	3.7707	0.7728

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 50 mg	0.41 (0.61) 51 (a)	0.98 (0.99) 51 A (d)	1.24 (1.09) 45 A	1.29 (1.12) 42 A	1.35 (1.09) 39 A	1.24 (1.12) 33 A	0.92 (1.09) 23 BC
Bromfenac 10 mg	0.41 (0.64) 51	0.92 (0.84) 50 A	1.37 (0.89) 47 A	1.35 (0.96) 45 A	1.35 (0.93) 42 A	1.25 (1.00) 36 A	1.20 (1.08) 33 A
Naproxen Na 550 mg	0.45 (0.64) 51	0.92 (0.98) 50 A	1.31 (1.05) 47 A	1.31 (1.09) 43 A	1.33 (1.19) 39 A	1.22 (1.19) 30 A	1.06 (1.17) 24 AB
Placebo	0.33 (0.52) 51	0.61 (0.78) 51 B	0.75 (0.93) 44 B	0.69 (0.97) 36 B	0.61 (0.90) 32 B	0.55 (0.94) 24 B	0.59 (0.98) 20 C
p-value Trt (b)	0.492	0.02	<0.001	<0.001	<0.001	<0.001	<0.001
p-value Trt*Period (b)	0.527	0.185	0.554	0.536	0.584	0.349	0.156
p-value Trt*Baseline (c)	0.445	0.831	0.961	0.97	0.888	0.819	0.483
Root MSE (b)	0.514	0.701	0.803	0.858	0.777	0.841	0.834

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + P(k) +Seq (l) + TP(ik) + error
(c) Model: PID = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
P=Period, Seq=Sequence

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted) **(Intent-to-Treat Patients)**
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF[a]

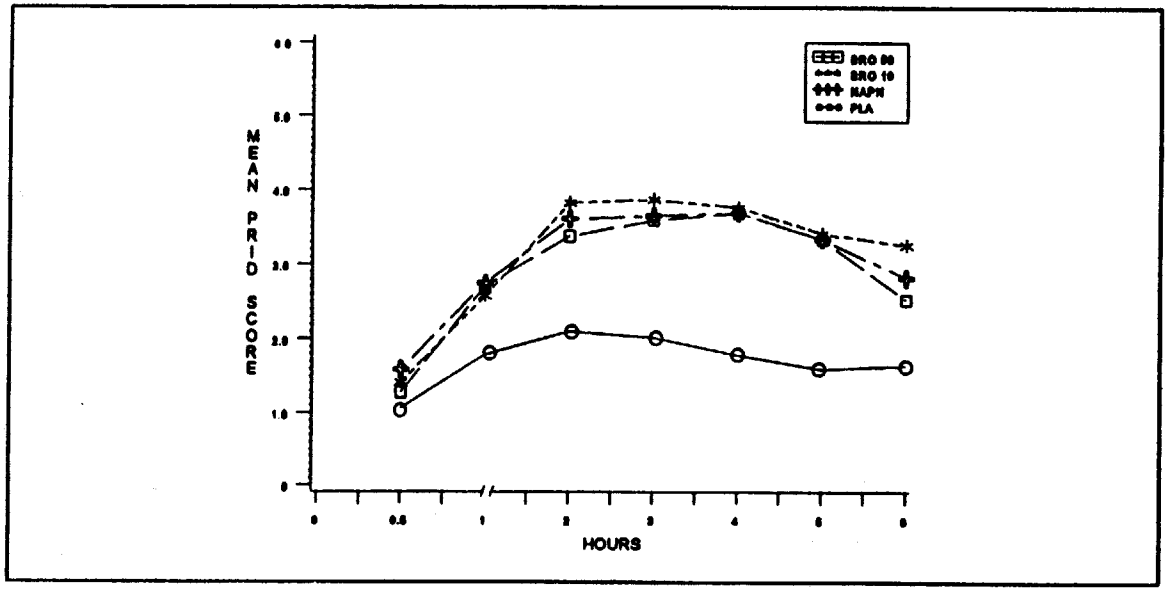
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain RELIEF
Bromfenac 50 mg	51	5.01A	11.39A	2.63A
Bromfenac 10 mg	51	5.44A	12.29A	2.86A
Naproxen Na 550 mg	51	5.40A	11.92A	2.82A
Placebo	51	3.26B	6.68B	1.90B
p-value Trt		0.0001	0.0001	0.0001
p-value Trt*Period		0.1891	0.1557	0.1275
Root MSE		2.8736	6.1740	1.2332

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)											
Treatment	1/2		1		2		3		4		5		6	
Bromfenac 50 mg	0.86 51 (a)	(1.06)	1.73 51	(1.51) A (d)	2.14 45	(1.60) A	2.29 42	(1.63) A	2.33 39	(1.67) A	2.10 33	(1.78) A	1.61 23	(1.80) BC
Bromfenac 10 mg	1.00 51	(1.25)	1.65 50	(1.35) A	2.45 47	(1.42) A	2.51 45	(1.39) A	2.41 42	(1.51) A	2.16 36	(1.68) A	2.06 33	(1.77) A
Naproxen Na 550 mg	1.14 51	(1.18)	1.82 50	(1.37) A	2.29 47	(1.54) A	2.33 43	(1.58) A	2.35 39	(1.65) A	2.12 30	(1.76) A	1.76 24	(1.77) AB
Placebo	0.73 51	(0.94)	1.18 51	(1.23) B	1.35 44	(1.47) B	1.33 36	(1.53) B	1.18 32	(1.49) B	1.04 24	(1.57) B	1.06 20	(1.65) C
p-value Trt (b)	0.074		0.019		<0.001		<0.001		<0.001		<0.001		<0.001	
p-value Trt*Period (b)	0.055		0.17		0.439		0.437		0.299		0.188		0.133	
p-value Trt* Baseline (c)	0.718		0.912		0.982		0.986		0.944		0.927		0.356	
Root MSE (b)	0.901		1.133		1.272		1.275		1.245		1.387		1.364	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + P(k) +Seq (l) + TP(ik) + error
(c) Model: PR = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
P= Period, Seq=Sequence

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID[a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	51	7.83A	17.91A	4.18A
Bromfenac 10 mg	51	8.39A	19.12A	4.51A
Naproxen Na 550 mg	51	8.28A	18.54A	4.49A
Placebo	51	4.98B	10.18B	3.02B
p-value Trt		0.0001	0.0001	0.0001
p-value Trt*Period		0.2230	0.2015	0.1645
Root MSE		4.4914	9.7151	1.9554

a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)													
	1/2		1		2		3		4		5		6	
Treatment														
Bromfenac 50 mg	1.27 51 (a)	(1.60)	2.71 51	(2.42) A (d)	3.37 45	(2.62) A	3.59 42	(2.68) A	3.69 39	(2.69) A	3.33 33	(2.85) A	2.53 23	(2.85) BC
Bromfenac 10 mg	1.41 51	(1.81)	2.57 50	(2.11) A	3.82 47	(2.22) A	3.86 45	(2.25) A	3.76 42	(2.36) A	3.41 36	(2.61) A	3.25 33	(2.78) A
Naproxen Na 550 mg	1.59 51	(1.71)	2.75 50	(2.23) A	3.61 47	(2.48) A	3.65 43	(2.57) A	3.69 39	(2.72) A	3.33 30	(2.86) A	2.82 24	(2.87) AB
Placebo	1.06 51	(1.38)	1.78 51	(1.91) B	2.10 44	(2.34) B	2.02 36	(2.45) B	1.78 32	(2.34) B	1.59 24	(2.48) B	1.65 20	(2.60) C
p-value Trt (b)	0.135		0.014		<0.001		<0.001		<0.001		<0.001		<0.001	
p- value Trt*Period (b)	0.131		0.196		0.473		0.466		0.422		0.256		0.15	
p-value Trt*Baseline (c)	0.583		0.903		0.994		0.983		0.996		0.93		0.415	
Root MSE (b)	1.341		1.764		2.024		2.084		1.962		2.178		2.149	

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + P(k) + Seq(l) + TP(ik) + error
(c) Model: PRID = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP(ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
P=Period, Seq=Sequence.

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Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	SD	n	Time (min)	95%-CI (min)
Bromfenac 50 mg	1.27	1.60	51	24	17-36
Bromfenac 10 mg	1.41	1.81	51	21	16-33
Naproxen Na 550 mg	1.59	1.71	51	19	14-27
Placebo	1.06	1.38	51	28	21-45

a Raw unadjusted mean of (unextrapolated) PRID scores.

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Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

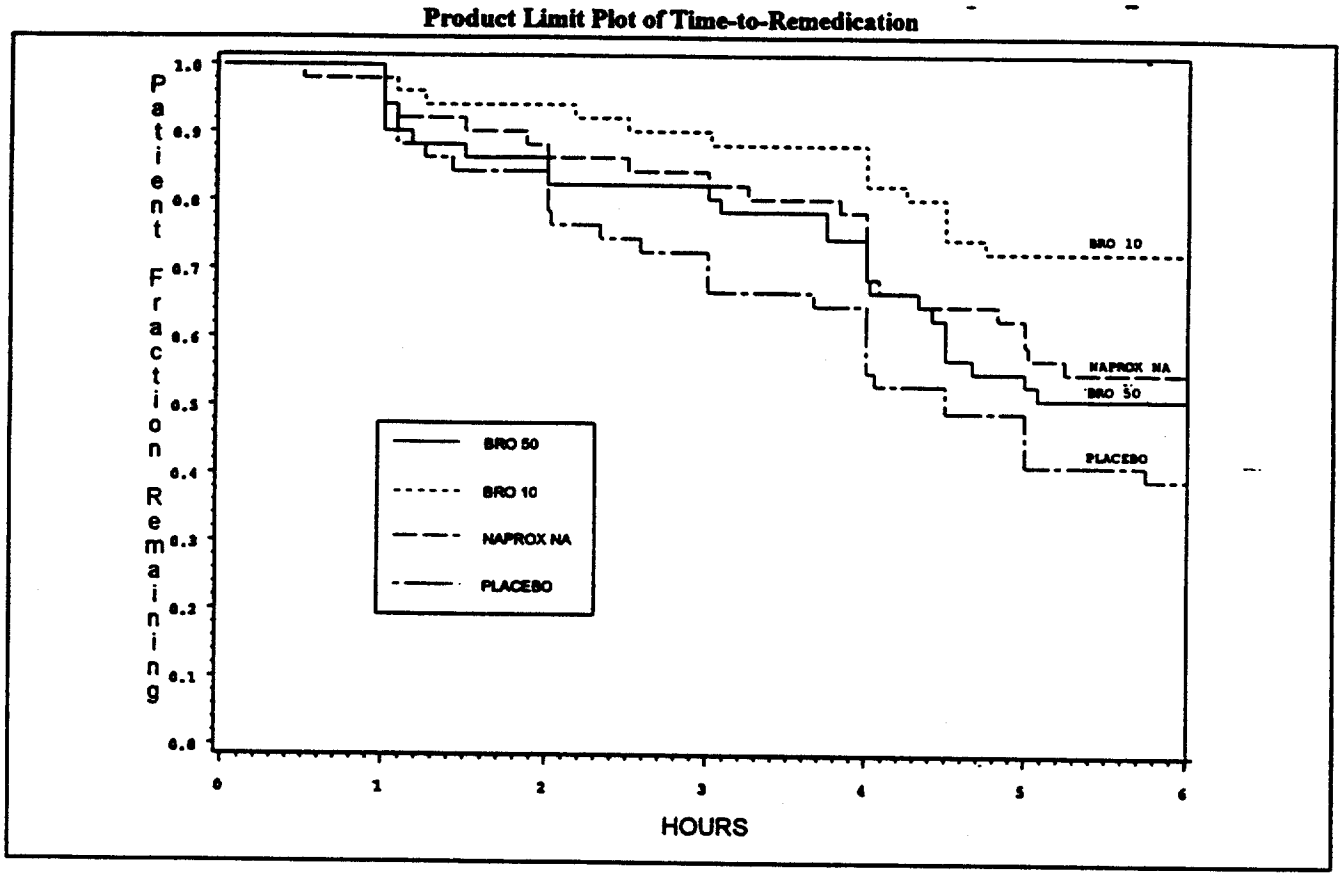


Table 5. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 50 mg	51	5:07 (B)[c]	(4:30, 5:43)
Bromfenac 10 mg	51	5:58 (A)	(5:28, >6h)
Naproxen Na 550 mg	51	5:24 (AB)	(4:51, 5:59)
Placebo	51	4:34 (B)	(3:56, 5:12)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg	3:45 (2:00, 4:30)	>6hr (4:25, >6hr)	>6hr (NE)
Bromfenac 10 mg	4:30 (4:00, >6hr)	>6hr (NE)	>6hr (NE)
Naproxen Na 550 mg	4:00 (3:00, 5:00)	>6hr (5:00, >6hr)	>6hr (NE)
Placebo	2:20 (1:25, 4:00)	4:30 (4:00, >6hr)	>6hr (NE)

NE: Not estimable.

Appendix II

CONFIDENTIAL: SBA Summary for Bromfenac Protocol 792-A-307-US

A Multiple-Dose Comparison of Bromfenac Sodium (AHR 10282B) 50 mg and 25 mg, Ibuprofen 400 mg and Placebo for the Treatment of Dysmenorrhea.

IND DRUG:	Bromfenac	DOSES:	50, 25 mg oral
REFERENCE DRUGS:	Ibuprofen Placebo	DOSE:	400 mg oral
TOTAL PTS ENROLLED:	54	DURATION OF DOSING:	Single dose, 6 hr Multiple dose, up to 3 days
INVESTIGATOR:	Benjamin Levy, M.D., Hartford, CT, United States		

PURPOSE: The present study was designed to demonstrate 1) the analgesic activity of bromfenac at single and multiple oral doses of 50 mg and 25 mg, and 2) to compare the analgesic efficacy of single and multiple doses of these bromfenac regimens to that of ibuprofen 400 mg in patients experiencing moderate or severe pain of primary dysmenorrhea, and 3) to assess the safety of these treatments in patients with primary dysmenorrhea.

METHOD: This was a single-center, double-blind, four-period crossover, placebo-controlled outpatient study comparing the efficacy and safety of bromfenac and ibuprofen for the relief of primary dysmenorrhea. Four treatment regimens of bromfenac 50 mg, bromfenac 25 mg, ibuprofen 400 mg, and placebo were assigned to women over the course of four menstrual cycles. Patients were instructed to take the first dose of study medication when the pain of dysmenorrhea was considered to be at least of moderate intensity. Repeat doses could be taken at least four hours apart, up to 4 times a day. Patients recorded their pain intensity and pain relief for 6 hours after the first dose and other efficacy assessments were recorded on the second day.

The primary efficacy variables were total pain relief (TOPAR, 3 and 6 hours), sum of pain intensity differences (SPID, 3 and 6 hours), and sum of pain relief plus pain intensity difference (SPRID, 3 and 6 hours). These variables were calculated from the area under the pain relief-, PID (pain intensity difference)-, and PRID (pain relief plus PID scores)- time curves, respectively by using the trapezoidal rule. Other variables were considered secondary for evaluation of efficacy (hourly pain relief, PID, and PRID scores, corresponding peak scores, dose 1 global and bedtime assessments, preference ratings, on-PRs and dur-PRs).

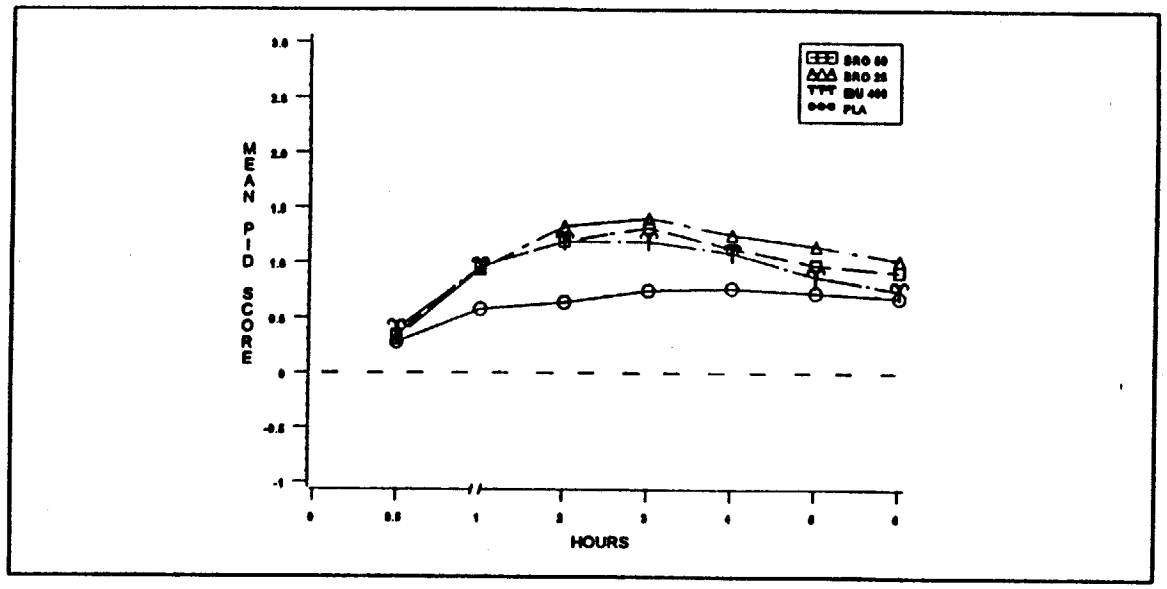
RESULTS: Fifty-four (54) women took the study medication at least once during the study and had data available for safety analysis. They ranged in age from 21 to 45 years (mean 32.5 years) and in weight from 42 to 113 kg (mean, 66.1 kg). Forty-seven (47) patients had data available for all 4 treatments and were used in the intent-to-treat efficacy analyses. Both doses of bromfenac were similar to ibuprofen 400 mg and significantly superior to placebo for all primary efficacy variables. Ibuprofen 400 mg was superior to placebo for peak pain relief, peak PRID, 3-hour SPID and SPRID. Bromfenac 50 mg and bromfenac 25 mg but not ibuprofen 400 mg were superior to placebo for dose 1 global and day 1 bedtime assessments. Only 10 patients had Day 2 efficacy data for all variables and all 4 periods; all 47 patients had preference rating data. The differences among treatments were not significant but the active treatments were numerically superior to placebo.

One or more TESE were reported by 22 (42%) patients who received bromfenac 50 mg, 24 (51%) patients who received bromfenac 25 mg, 16 (33%) patients who received ibuprofen 400 mg, and 15 (31%) patients who received placebo. Two (2) patients (1 patient taking bromfenac 50 mg and 1 patient taking placebo) withdrew from the study because of adverse events that were classified by the investigator as drug-related. These events resolved after treatment was discontinued. One (1) patient withdrew from the study because of serious study events, metrorrhagia, abdominal pain and uterine fibroids, that were considered unrelated to study drug.

CONCLUSIONS: Both doses of bromfenac were consistently statistically distinguishable from placebo; ibuprofen was superior to placebo in 2 of 6 primary variables. The results indicate that doses of 50 mg and 25 mg of bromfenac may be more effective than ibuprofen 400 mg in providing relief from pain due to dysmenorrhea. The tolerance of all treatments was comparable and acceptable.

Figure 1, Table 1. Mean Scores of Pain Intensity Differences (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL SPID AND PEAK PID [a]

Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	47	2.74A	5.96A	1.47A
Bromfenac 25 mg	47	2.89A	6.51A	1.49A
Ibuprofen	47	2.70A	5.63AB	1.43AB
Placebo	47	1.58B	3.78B	1.00B
p-value Trt		0.0088	0.0109	0.0190
p-value Trt*Period		0.2045	0.3028	0.1245
Root MSE		2.0851	4.3453	0.8727

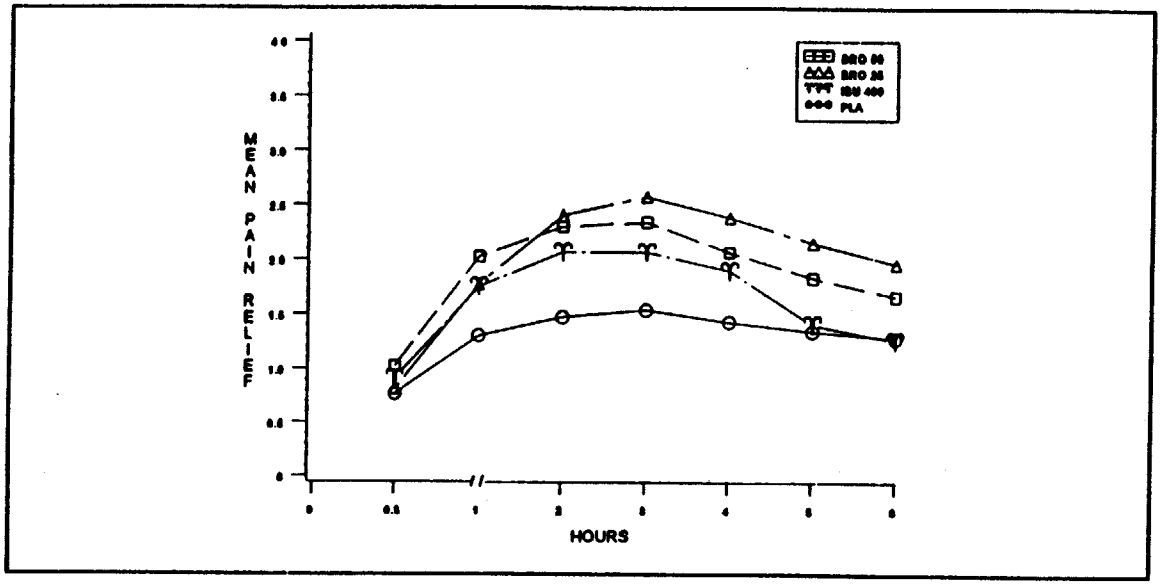
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 50 mg	0.34 (0.70) 47 (a)	0.96 (1.02) 47	1.19 (1.01) 40 A (d)	1.32 (1.02) 37 A	1.13 (1.06) 33 A	0.98 (1.17) 27	0.91 (1.19) 23
Bromfenac 25 mg	0.31 (0.62) 45	0.94 (0.99) 47	1.33 (0.99) 37 A	1.40 (0.95) 35 A	1.26 (1.01) 30 A	1.15 (1.02) 25	1.02 (0.99) 21
Ibuprofen 400 mg	0.39 (0.74) 46	0.96 (1.00) 46	1.19 (1.06) 37 A	1.19 (1.08) 33 A	1.09 (1.06) 28 AB	0.87 (1.10) 19	0.74 (1.07) 16
Placebo	0.28 (0.74) 47	0.57 (0.95) 47	0.64 (1.01) 35 B	0.74 (1.07) 27 B	0.77 (0.98) 19 B	0.72 (0.99) 14	0.68 (1.00) 13
p-value Trt (b)	0.924	0.101	0.001	0.001	0.026	0.077	0.136
p-value Trt*Period (b)	0.899	0.321	0.096	0.358	0.436	0.433	0.289
p-value Trt*Baseline (c)	0.926	0.847	0.786	0.887	0.563	0.742	0.899
Root MSE (b)	0.613	0.884	0.898	0.903	0.855	0.896	0.864

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + P(k) + Seq(l) + TP(ik) + error
(c) Model: PID = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP (ik) + error
P=Period, Seq=Sequence.
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Figure 2, Table 2. Pain Relief (Extrapolated, Unadjusted)
Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically)

(Intent-to-Treat Patients)



3-HOUR AND FINAL TOPAR AND PEAK RELIEF [a]

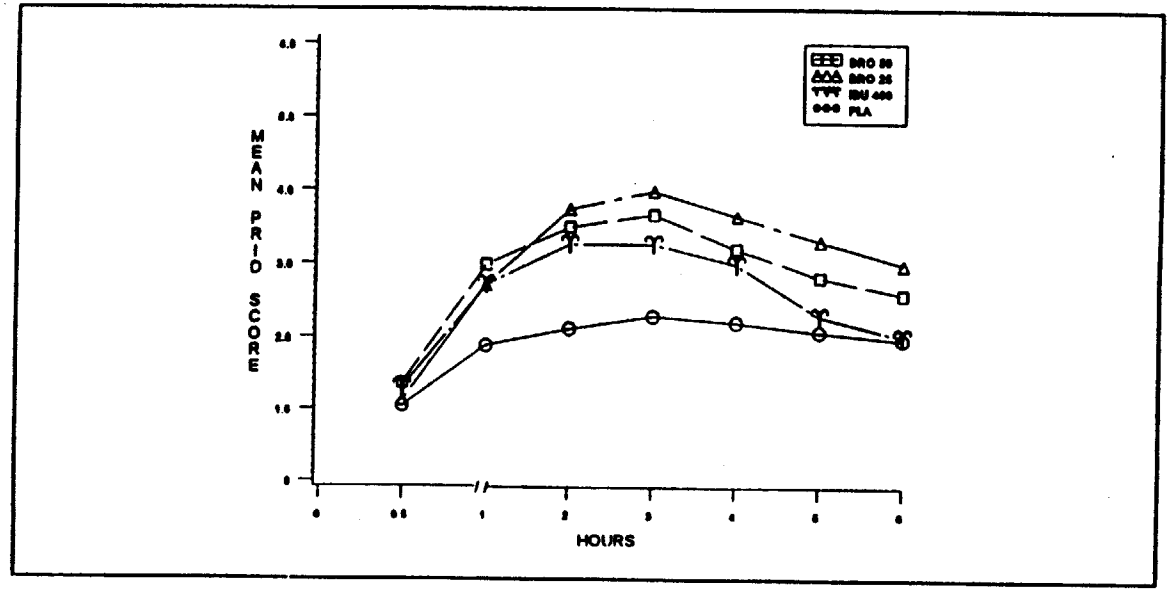
Treatment Group	n	3-hour TOPAR	Final TOPAR	Peak Pain RELIEF
Bromfenac 50 mg	47	5.49A	11.39A	2.66A
Bromfenac 25 mg	47	5.42A	12.22A	2.66A
Ibuprofen	47	4.86AB	9.81AB	2.43A
Placebo	47	3.59B	7.76B	1.83B
p-value Trt		0.0249	0.0150	0.0194
p-value Trt*Period		0.2173	0.1863	0.0800
Root MSE		3.3517	7.0776	1.4181

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 50 mg	1.02 (1.15) 47 (a)	2.02 (1.44) 47	2.30 (1.57) 40 A (d)	2.34 (1.61) 37 A	2.06 (1.69) 33 A	1.83 (1.80) 27 AB	1.66 (1.86) 23
Bromfenac 25 mg	0.81 (0.99) 45	1.77 (1.45) 47	2.40 (1.54) 37 A	2.57 (1.61) 35 A	2.38 (1.66) 30 A	2.15 (1.73) 25 A	1.96 (1.71) 21
Ibuprofen 400 mg	0.90 (1.11) 46	1.74 (1.42) 46	2.06 (1.51) 37 A	2.06 (1.51) 33 AB	1.89 (1.55) 28 AB	1.40 (1.68) 19 B	1.26 (1.66) 16
Placebo	0.77 (1.18) 47	1.30 (1.33) 47	1.47 (1.57) 35 B	1.53 (1.63) 27 B	1.43 (1.64) 19 B	1.34 (1.68) 14 B	1.28 (1.66) 13
p-value Trt (b)	0.624	0.067	0.011	0.004	0.010	0.024	0.065
p-value Trt*Period (b)	0.841	0.490	0.112	0.175	0.271	0.123	0.253
p-value Trt*Baseline (c)	0.954	0.921	0.859	0.854	0.698	0.760	0.672
Root MSE (b)	0.986	1.339	1.462	1.433	1.414	1.442	1.422

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + P(k) + Seq (l) +TP(ik) + error
(c) Model: PR = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP (ik) + error
(d) Fisher's Protected LSD based on Model (b) LSMEANS
P=Period, Seq=Sequence.

Figure 3, Table 3. Mean Scores of Pain Relief Combined with Pain Intensity Differences (Extrapolated, Unadjusted) Means (Standard deviations), Sample Sizes without Extrapolation, and Fisher's Protected LSD Comparisons (Vertically) **(Intent-to-Treat Patients)**



3-HOUR AND FINAL SPRID AND PEAK PRID [a]

Treatment Group	n	3-hour SPRID	Final SPRID	Peak PRID
Bromfenac 50 mg	47	8.23A	17.35A	4.11A
Bromfenac 25 mg	47	8.31A	18.72A	4.13A
Ibuprofen	47	7.56A	15.44AB	3.85A
Placebo	47	5.17B	11.54B	2.83B
p-value Trt		0.0137	0.0116	0.0182
p-value Trt*Period		0.2083	0.2329	0.0826
Root MSE		5.3091	11.2496	2.2447

a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means presented in the tables are unadjusted and therefore different from the summaries included in the December 1994 NDA submission.

	Assessment Time Points (Hours)						
Treatment	1/2	1	2	3	4	5	6
Bromfenac 50 mg	1.36 (1.75) 47 (a)	2.98 (2.33) 47	3.49 (2.46) 40 A (d)	3.66 (2.53) 37 A	3.19 (2.67) 33 A	2.81 (2.90) 27 AB	2.57 (3.00) 23
Bromfenac 25 mg	1.12 (1.47) 45	2.70 (2.33) 47	3.73 (2.46) 37 A	3.98 (2.50) 35 A	3.64 (2.62) 30 A	3.30 (2.69) 25 A	2.98 (2.63) 21
Ibuprofen 400 mg	1.30 (1.78) 46	2.70 (2.34) 46	3.26 (2.50) 37 A	3.26 (2.50) 33 AB	2.98 (2.52) 28 AB	2.28 (2.72) 19 B	2.00 (2.69) 16
Placebo	1.04 (1.85) 47	1.87 (2.21) 47	2.11 (2.52) 35 B	2.28 (2.63) 27 B	2.19 (2.58) 19 B	2.06 (2.64) 14 B	1.96 (2.63) 13
p-value Trt (b)	0.728	0.066	0.004	0.002	0.012	0.034	0.082
p-value Trt*Period (b)	0.856	0.411	0.111	0.237	0.337	0.221	0.279
p-value Trt*Baseline (c)	0.965	0.884	0.834	0.862	0.660	0.766	0.767
Root MSE (b)	1.506	2.142	2.310	2.283	2.226	2.301	2.249

(a) Sample sizes, not extrapolated
(b) Model: PRID = u + T(i) + B(j) + P(k) + Seq(l) +TP(ik) + error
(c) Model: PRID = u + T(i) + B(j) + P(k) + Seq(l) + TB(ij) + TP (ik) + error
P=Period, Seq=Sequence.
(d) Fisher's Protected LSD based on Model (b) LSMEANS

Table 4. Estimated Onset of Pain Relief (on-PR)

	PRID at 30 min			Estimated on-PR	
Treatment Group	Mean [a]	SD	n	Time (min)	95%-CI (min)
Bromfenac 50 mg	1.36	1.75	47	22	16-35
Bromfenac 25 mg	1.13	1.50	45	26	19-44
Ibuprofen 400 mg	1.28	1.80	46	23	17-40
Placebo	1.04	1.85	47	29	19-60

a Raw unadjusted mean of (unextrapolated) PRID scores.

Figure 4. Estimated Duration of Analgesia
(Time-to-Remedication)

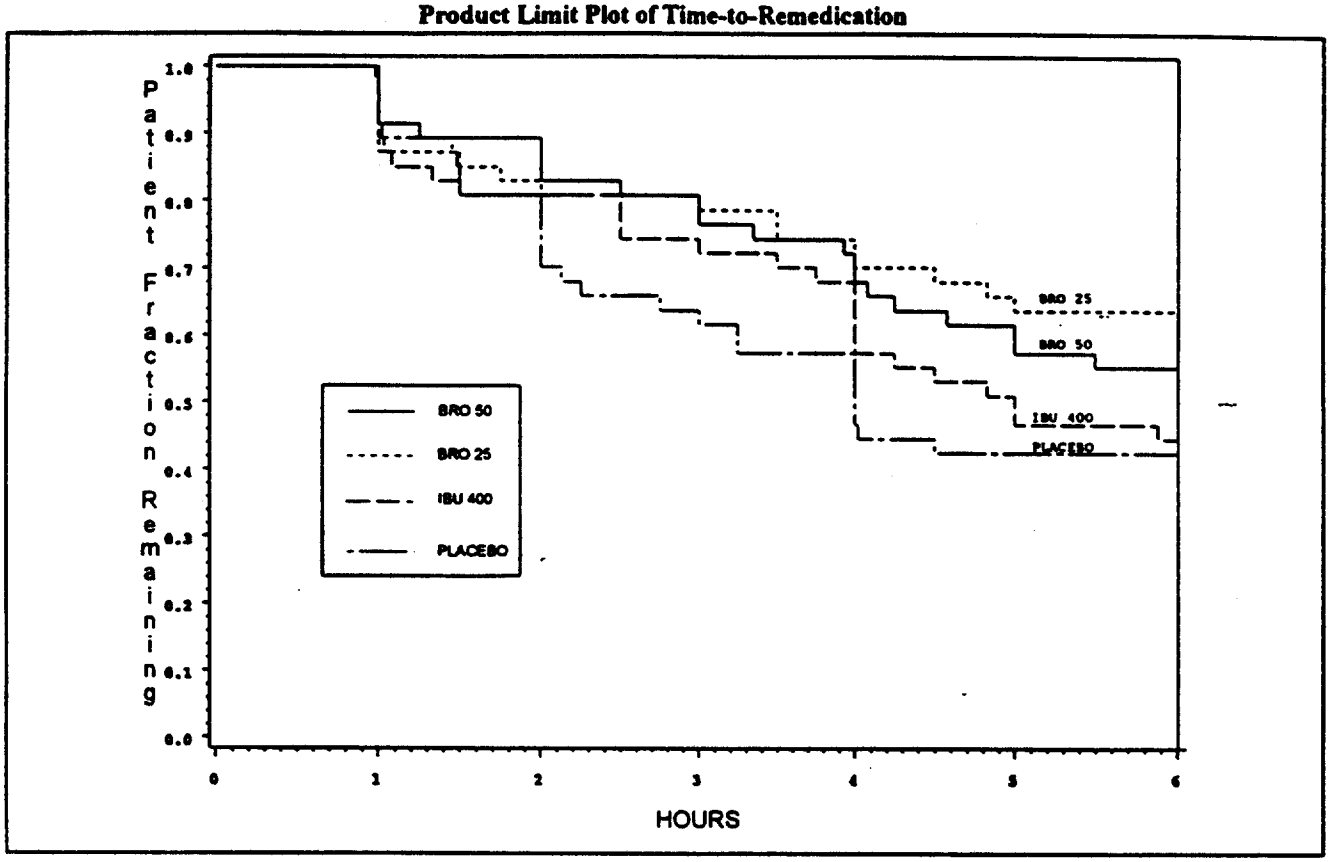


Table 5. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 50 mg	47	5:17 (AB)[c]	(4:40, 5:56)
Bromfenac 25 mg	45	5:36 (A)	(4:58, > 6h)
Ibuprofen 400 mg	46	4:57 (AB)	(4:18, 5:36)
Placebo	47	4:28 (B)	(3:46, 5:10)

(a) Kaplan-Meier estimate (Ref: Lee, Statistical Methods for Survival Data Analysis, 2nd edition, pg. 77).
(b) Confidence intervals are based on the z-distribution and utilize the standard error of (a).
(c) Logrank test applied.

Table 6. Time-to-Remedication (Percentiles)

Treatment Group	----------Percentiles In Hours:minutes (95% C. I.)----------		
	25%	50% (Median)	75%
Bromfenac 50 mg	3:56 (2:00, 5:00)	>6hr (4:35, >6hr)	>6hr (NE)
Bromfenac 25 mg	4:00 (1:45, >6hr)	>6hr (NE)	>6hr (NE)
Ibuprofen 400 mg	3:30 (1:30, 4:00)	5:00 (4:00, >6hr)	>6hr (NE)
Placebo	2:00 (1:29, 3:15)	4:00 (3:00, >6hr)	>6hr (NE)

NE: Not estimable.

Bromfenac Clinical Pharmacology Studies

MEDICAL OFFICER REVIEW

NDA #: 20-535
NAME: Bromfenac Sodium.
SPONSOR: Wyeth-Ayerst
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: December 19, 1995.
CSO: C. Koerner

This review covers the four studies done under the IND to explore bromfenac's clinical pharmacology, excluding PK studies. One study looked at effect on platelet function, one looked at GI blood loss, and two investigated effects on dermal erythema. A brief inventory appears below followed by study synopses:

Study Number	N	Objective	Results
07 (sec. 1)	4	platelet aggregation	Reversible effect lasting <24 hrs
07 (sec. 2)	12	bleeding time	No signif. effect with bromfenac or aspirin.
14	45	fecal blood loss	Bromfenac increased blood loss over baseline, but less than aspirin.
09	12	prevention of UV-induced erythema	No effect, insensitive study.
17	6 pilot 16 fed/fast	suppression of nicotinate-induced erythema	Aspirin seemed effective, but effect was not as clear for bromfenac, inconsistent food effect.

STUDY 07: PLATELET EFFECTS

This study had three sections, the first and last involved the same patients, and are considered together under section 1.

Section 1

Design: This was an open-label study in 4 volunteers. Each subject was given a 100 mg dose of bromfenac. Measurement of platelet aggregation (in response to collagen) and thromboxane B2 (TxB2) was done at 20 and 40 minutes, and at 1, 2, 4, 7 and 24 hours after dosing.

Effects on platelet aggregation are show in the following table:

Platelet Aggregation Inhibition (in %)

Collagen	Time after Dose						
(µg/mL)	20 min	40 min	1 hr	2 hr	4 hr	7 hr	24 hr
5	75	97	96	95	94	82	-12
10	70	93	93	88	89	57	-7
20	53	75	69	73	72	41	3
50	33	49	48	44	43	25	4

Inhibition of platelet aggregation was maximal at 40 min. Although some platelet inhibition persisted past 7 hours, the effect was gone by 24 hours. When the study was repeated in the same 4 subjects using 325 mg aspirin (section 3), inhibition at 24 hours was similar to that at 1 hour. An effect on TxB2 was also seen; concentrations were minimized at 20 min after the dose.

Section 2:

Design: This was a double-blind, placebo- and active-controlled 6-way crossover study in 14 volunteers. Treatments consisted of placebo, aspirin 325 mg, bromfenac 1, 5, 25, and 125 mg. Placebo and aspirin were randomly assigned in periods 1 and 2 each followed by 14-day washout. The various bromfenac doses were randomized in the last 4 periods, each followed by 7-day washout. Bleeding time, blood loss, and TxB2 concentrations were measured at baseline and at 1 hour post dose.

Results are shown in the following table:

			Bromfenac				ASA
		Placebo	1 mg	5 mg	25 mg	125 mg	325 mg
bleeding time (min)	baseline	5.1	5.6	4.6	5.1	4.9	5.3
	1 hour	5.5	5.5	5.6	6.6	6.5	6.8
blood loss (µL)	baseline	54	54	43	50	39	42
	1 hour	57	53	58	69	54	86
TxB2 conc.	baseline	110	137	147	154	132	132
	1 hour	109	67*	15*	16*	0*	0*

*All 1-hour TxB2 concentrations were less than placebo at p<.05 (the 1 mg comparison involved only 3 subjects).

The bleeding time and blood loss studies did not show any effect of bromfenac, but the studies were insensitive to aspirin as well. There was an effect on TxB2 production that exhibited a dose response (although 5 vs. 25 mg showed a reversal).

STUDY 14: FECAL BLOOD LOSS

Design: This was a randomized, double-blind, placebo- and active-controlled parallel study in 45 volunteers aged 21 to 43. Treatments were placebo, bromfenac 75 mg qid or aspirin 975 mg qid. During a 2-day admission period, red cells were labeled with chromium 51. This was followed by 7 days of treatment with single-blind placebo. Subjects with less than 2 mL/day fecal loss in the last 4 days were randomized to treatment for 10 days (days 10-19) Blood loss was estimated using radioactivity counts on blood samples from days 16-19 and stool samples from days 17-20.

Results: Of 45 initial subjects, 37 were entered into the treatment period (12 placebo, 12 bromfenac, 13 aspirin). One aspirin subject was discontinued after 7 days of treatment due to elevated liver enzymes, leaving 12 in each group. Results are tabulated below:

Treatment	Mean Fecal Blood Loss (mL/day) ± S.D.		
	Baseline	On Treatment	Change
Placebo (N=12)	0.5 ± 0.3	0.4 ± 0.1	-0.1 ± 0.2
Bromfenac 75 mg qid (N=12)	0.5 ± 0.2	2.1 ± 1.1	1.6 ± 1.0*+
Aspirin 975 mg qid (N=12)	0.4 ± 0.2	8.8 ± 4.1	8.3 ± 4.2*

* Significantly greater than Placebo.
+ Significantly less than Aspirin.

Both aspirin and bromfenac produced an increase in fecal blood loss, but the average increase due to bromfenac was smaller.

STUDY 09: PREVENTION OF UV-INDUCED ERYTHEMA

This study had two sections, the first used two doses of bromfenac, the second used an active control.

Section I

Design: This was a randomized, double-blind, placebo-controlled, 3-way crossover study in 12 white male volunteers. Treatments were single doses of placebo, bromfenac 10 mg, or bromfenac 25 mg, each given fasted. At 1 hour after the dose, skin patches on the back of each subject were irradiated with UV-B for a variety of pre-selected time intervals ranging from 8 to 95 seconds. A trained observed assessed erythema at 6 and 24 hours. The endpoint for each subject was the minimal exposure that produced erythema.

Results: No erythema was detected at 6 hours. At 24 hours the three treatments had nearly identical results, with average exposures ranging from 33.2 ± 3.6 sec for placebo to 34.7 ± 3.0 sec for bromfenac 25 mg.

Section II

Design: This was a randomized, double-blind, placebo- and active-controlled, 3-way crossover study in 12 white male volunteers (10 were the same as in section I). Treatments were four doses, given q4h without food, of placebo, bromfenac 50 mg, or indomethacin 50 mg. UV-B exposure was given 1 hour after the first dose. The endpoint was the same as in section I.

Results: There was no erythema at 6 hours. At 24 hours the three treatments were nearly identical, with exposures ranging from 36.3 ± 2.6 min for placebo to 38.5 ± 3.6 min for indomethacin.

STUDY 17: SUPRESSION OF NICOTINATE-INDUCED ERYTHEMA

This study had two similar sections. The first was a pilot study with one dose of bromfenac. The second was an incomplete crossover study with several doses. The sponsor did not provide statistical analysis beyond simple tabulation. The description of the study designs and results are combined:

Design: These were randomized, double-blind, placebo- and active-controlled crossover studies in volunteers. Section I used 6 subjects in a complete crossover comparison of single doses of placebo, bromfenac 25 mg and aspirin 650 mg, all given without food. In section II the treatments were placebo fasted, aspirin 650 mg fasted, bromfenac 5, 10 or 25 mg fasted, and bromfenac 5, 10 or 25 mg given with food. Section II used 16 subjects but in a 3-period incomplete crossover, so that each treatment was received by 6 subjects. One hour after dosing, nicotinate ointment 0.5%, 1.5% and 3.0%, were applied. Assessments were made at 1, 1.25, 1.5, 1.75, 2, 2.5 and 3 hours. In section I, assessments were made of erythema, skin temperature, and edema. In section II, assessments were made of erythema and cutaneous blood flow measured by laser Doppler.

Results: (No statistical hypothesis testing results were provided; the following description of results refers only to numerical differences in averages, not the results of statistical testing.) In section I bromfenac did not seem to affect erythema, but it seemed to lower initial skin temperature. The edema response was not consistent and therefore not considered useful. In section II aspirin seemed to inhibit the effect of nicotinate, and bromfenac appeared much less effective. The effect of food appeared to be inconsistent for the different doses of nicotinate.

CONCLUSIONS:

Bromfenac affects platelet function as measured by collagen-induced aggregation. Like most other NSAIDs (but unlike aspirin) the effect on platelets is reversible. The effect of a large single dose is still discernible at 7 hours but disappears by 24 hours It is noteworthy that the effect appears to outlast the plasma concentration, a phenomenon that also is seen with the analgesic effect. An effect of bromfenac on bleeding times could not be demonstrated, but that study could not demonstrate the effect of aspirin either.

Bromfenac does increase fecal occult blood loss (which could reflect platelet dysfunction, GI toxicity, or both), when bromfenac is given at 300 mg/day for 10 days. The blood loss was less than that produced by aspirin 3900 mg/day for 10 days.

Bromfenac's effect on the dermal erythema response to noxious stimuli was not demonstrated. The study using UV irradiation was insensitive. The nicotinate study was small and was not analyzed statistically, but seemed to show at most a weak effect of up to 25 mg of bromfenac.

RECOMMENDATIONS
The results of the fecal blood loss study may be described in the labeling, but there should be a qualification that the clinical significance is unknown.

The sponsors proposed labeling includes the following: "[Tradename] inhibits platelet aggregation and may prolong bleeding time. Unlike with aspirin, the inhibition of platelet function disappears with 24 hours." These statements are supported and should appear in the labeling.

John E Hyde

John E. Hyde, Ph.D., M.D

Russ. Widmark 12-26-95

Bromfenac Safety Summary

MEDICAL OFFICER REVIEW

NDA #: 20-535
NAME: Bromfenac Sodium
SPONSOR: Wyeth-Ayerst
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.
REVIEW DATE: December 19, 1995.
CSO: C. Koerner

TOTAL EXPOSURE TO BROMFENAC

Of 3762 patients in therapeutic trials in the NDA, 2402 were exposed to bromfenac. The breakdown by study type is given below:

Study Type	Patients	Total Exposure
Analgesia	1071	
Multiple dose	384	1594 pt-days
Dysmenorrhea	245	227 pt-days
Chronic (OA & RA)	926	5948 pt-months

The cumulative chronic exposure from the OA and RA studies is set out below:

Cumulative Exposure in Chronic Studies (initial N=926)

≥ 31 days	≥ 61 days	≥ 91 days	≥181 days	≥ 271 days	> 360 days
799	638	578	474	291	193

A more detailed breakdown of the chronic study exposure is provided in sponsor's table 3.8 from vol. 1.252, p. 48, which is reproduced in the appendix on page 8. Of note from that table is that for doses of 200 mg/day and above, 197 patients were exposed initially and 164 were exposed for a month or more.

DEATHS

The only deaths reported were two cardiovascular deaths in OA studies. One was in the open-label extension of Study 309. The other was in the second segment of Study 314, which was ongoing at the time the submission was prepared.

No deaths were reported from the clinical pharmacology (including PK) studies, single-dose or short-term analgesia studies, dysmenorrhea studies or RA studies. There were no reports of foreign deaths; the drug is not approved in any foreign country.

Descriptions of the fatal cases are as follows:

Patient 30918-022 was a 74 year old male with a history of hypertension, coronary artery disease, mild CHF and hematochezia. He was enrolled in Study 309, a two-segment comparison of bromfenac and ibuprofen in OA with an open-label extension. He received placebo in segment I, ibuprofen for 366 days in segment II, and bromfenac 150 mg/d for 286 days in the open-label extension. He was hospitalized and medication stopped for unrelenting back pain, and he expired the next day. Autopsy found a ruptured abdominal aneurysm.

Patient 31411-001 was a 76 year old male with a history of labile hypertension, renal insufficiency secondary to diuretics, peripheral edema, depression, and phlebitis and cellulitis of the legs. He was enrolled in Study 314, an ongoing OA study. He dropped out of segment I due to unsatisfactory response, then entered segment II and received bromfenac 50 mg/d for 50 days and 75 mg/day for 28 days. One evening he complained of severe indigestion, then collapsed and died. The death certificate listed acute myocardial infarction; there was no autopsy.

It is unlikely that either of these deaths were related to bromfenac.

NEOPLASMS

There were no new neoplasms reported in the single- or multi-dose analgesia studies, the PK studies, or the other pharmacology studies. One case of uterine fibroids was reported in a patient in the dysmenorrhea studies. In the chronic studies (OA and RA) there were 26 reported neoplasms, 19 of which occurred in bromfenac-treated patients. Seven of those were diagnosed as benign or were probably benign since they resolved spontaneously.

The numbers of cases and crude rates are tabulated below:

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Neoplasms Reported in Chronic Studies (OA and RA)

	Patients Exposed	Number of Neoplasms	Crude Rate
Any Bromfenac Dose	926	19	2.1 %
Bromfenac mg/day:			
200-225	197	1	0.5 %
150-199	119	5	4.2 %
76-149	516	13	2.5 %
<75	94	0	0.0 %
Ibuprofen	159	6	3.8 %
Naproxen	83	1	1.2 %
Diclofenac	78	0	0.0 %
Aspirin	45	0	0.0 %

Brief descriptions of each case were provided in the sponsor's Table 5.33 from vol. 1.252, p. 175, which is reproduced in the appendix on pages 9-11. Given the demographics of the study population, the types of neoplasms found in bromfenac patients were not unexpected. The overall crude rate for bromfenac is in line with that for ibuprofen and naproxen (note that naproxen and aspirin were used only in 6-week studies).

Evidence from the human studies does not identify any particular neoplastic risk for bromfenac.

ALLERGIC REACTIONS

Data from three types of regimens were provided in the NDA: single short-term exposure (1-7 days) from analgesia studies, repeated short exposures from dysmenorrhea studies, and chronic exposure from OA and RA studies.

In single dose analgesia studies 1072 patients were exposed to bromfenac, and an additional 384 patients were exposed for an average of 4 days in multi-dose analgesia studies. In the bromfenac treated patients there were 6 reports of allergic reactions: 2 were urticaria, 3 involved edema, one was a skin reaction attributed to penicillin. Among all treatments, there were 5 cases of urticaria: 2 with bromfenac, 1 with ibuprofen and 2 with placebo. Brief descriptions of these events were provided in sponsor's table 5.22 on p. 156 of vol. 1.252. That table is reproduced on page 12 of the appendix

In the dysmenorrhea studies, 239 patients were exposed to bromfenac in two separate periods. The only allergic events reported in the first exposure in these patients were 5 cases of sinus congestion, 2 cases of seasonal allergies, and 2 cases of nasal congestion. The second exposure netted 2 cases of seasonal allergies and 1 case of nasal congestion. There were no hypersensitivity-type reactions (Table 5.LL vol. 1.256 p. 379).

A total of 926 patients were exposed to bromfenac in chronic studies of OA or RA, and a total of 21 allergic adverse events were reported. Data in the table below are abstracted from sponsor's Table 5.23 from vol. 1.252 p. 159. Table 5.24, vol. 1.252 p. 160-163 gives brief case descriptions; it is reproduced on pages 13-16 of the appendix.

Numbers of Allergic Adverse Events in Chronic Studies (OA and RA)

	Patients Exposed	Any Rxn (%)	Allerg Rxn	Face Edema	Asthma	Urti-caria	Angio-edema	Other
Any Bromfenac Dose	926	21 (2.2)	5	5	3	7	1	1
Bromfenac mg/day:								
200-225	197	5 (2.5)	1	0	2	2	0	0
50-199	119	3 (2.5)	0	1	0	2	0	0
6-149	516	10 (1.9)	4	2	1	2	1	1
<75	94	3 (3.2)	0	2	0	1	0	0
Ibuprofen	159	7 (4.4)	0	0	4	2	1	0
Naproxen	83	0 (0.0)	0	0	0	0	0	0
Diclofenac	78	1 (1.3)	0	0	0	1	0	0
Aspirin	45	1 (1.2)	0	1	0	0	0	0

All three of the patients who reported asthma while on bromfenac had asthma before the study. The report of angioedema was angioedema of the arm.

The data indicate that bromfenac can be involved in allergic reactions. The frequency was not out of line with the comparator NSAIDs (naproxen and aspirin were used only in 6-week studies). None of the allergic adverse events appeared particularly worrisome. The exposed population was too small for one to expect to see significant rare events such as anaphylaxis or anaphylactoid reactions.

PERFORATIONS, ULCERS AND BLEEDS (PUBs)

The sponsor reviewed cases with study event COSTART terms suggesting PUBs. Twenty-six cases were identified from the chronic studies including seven identified from follow-up data that were not part of the study even data base. Nineteen of the cases were associated with bromfenac. One case was also reported from one of the drug interaction studies. No cases were found in the analgesia or dysmenorrhea studies. There were no perforations.

The case from the interaction study was as follows:

> A 34 year old male volunteer received bromfenac 50 mg t.i.d. for 4 days followed by 13 days of warfarin. He experienced hematemesis and melena, and endoscopy found a

bleeding duodenal ulcer. Hgb dropped to 5.4 vs. 14 at entry. He was stabilized after treatment including transfusion.

The 19 cases in the chronic studies included the following diagnoses: 6 gastric ulcers, 4 duodenal ulcers, 2 esophageal ulcers, 2 cases of duodenitits/gastritis, 2 cases of hemorrhoids/proctitis and 4 cases classified as inconclusive. The latter were clearly GI bleeds, but without cause being established. These were 2 cases of melena, a case a hematemesis and a case of hematochezia. Sponsor's Table 5.14, vol. 1.252 p. 140-145 provides brief descriptions of PUB cases; it is reproduced on pages 17-22 of the appendix.

In addition to crude rates (Tables 5.12 and 5.13 on p. 137 and 138 of vol. 1.252), the sponsor also computed lifetable rates for PUBs (vol. 1.256, p. 370-378):

Lifetable Estimates of PUB Rates in Chronic Studies (OA and RA)

		Cumulative probability (as percent) ± standard error			
	Patients Exposed	by 31 days	by 91 days	by 181 days	by 361 days
Any Bromfenac Dose	926	0.0 ± 0.0	0.8 ± 0.3	1.3 ± 0.4	2.7 ± 0.8
Bromfenac mg/day					
200-225	197	0.0 ± 0.0	2.4 ± 1.2	3.2 ± 1.4	4.7 ± 2.0
150-199	119	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	6.3 ± 3.1
76-149	516	0.0 ± 0.0	0.5 ± 0.3	1.0 ± 0.5	1.0 ± 0.5
<75	94	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Ibuprofen	159	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	1.1 ± 1.1
Diclofenac	78	0.0 ± 0.0	1.4 ± 1.4	1.4 ± 1.4	6.1 ± 4.8

Naproxen and Aspirin had no PUB events and so are not included in the table. Both were used only in 6-week studies.

There is the suggestion of a dose-response for bromfenac, but it is interrupted by the delayed occurrence of PUBs in the 150-199 mg/day group. Comparisons are difficult due to the low numbers of events and the fact that pooling events means that comparisons cross study lines. The data suggest that the PUB risk for bromfenac is somewhere in the range represented by ibuprofen and diclofenac, i.e., bromfenac appears to be typical of the "NSAID class" with regard to PUBs.

HOSPITALIZATIONS

In this section, hospitalizations refers to new hospitalizations due to study events. Patients already hospitalized in the surgical analgesia trials were not included.

There were no hospitalizations in the analgesia studies. A 40 year old female in dysmenorrhea study 307 was hospitalized for hysterectomy for fibroids. In the chronic studies, 61 patients were hospitalized. Reasons are provided in sponsor's table 5.30 from vol. 1.252 p. 168-170, which is included in the safety appendix on pages 23-25. There were several hospitalizations for GI bleeding, but these also were included in the PUB section above. The vast majority of the remaining hospitalizations were events not unexpected in the OA/RA patient population. Of note, however, are two cases of pancreatitis. One, in a 52 year old female in study 303, was a case of acute biliary pancreatitis, but the other had no clear etiology (vol. 1.257, p. 91):

> Patient 30321-010, was a 61 year old female enrolled in OA study 303. She had taken bromfenac 25 mg q.i.d for 42 days in the double-blind segment, and bromfenac 50 mg b.i.d. for 68 days when she was hospitalized for acute pancreatitis. She also received triamterine/hydrochlorothiazide, cefuroxine axetil, flunisolide, and theophylline. Mild elevations of SGOT and SGPT were present at weeks 2 and 6. Uric acid was mildly elevated at 2.5 months. The investigator's assessment was that the pancreatitis was not related to study medication.

CLINICAL LABORATORY FINDINGS

The clinical laboratory findings are reviewed separately. Of note are the findings for liver enzymes. Although the incidence of any liver enzyme elevations was fairly typical for NSAIDs, the incidence of significant elevations appeared especially high, and the significant elevations occurred as soon as about 1 month after starting treatment.

CONCLUSIONS:

The profile of serious adverse events for bromfenac appears to be similar to that of other NSAIDs except for its hepatic toxicity. The incidence of PUBs and allergic reactions appears to be in line with that expect for the NSAID class. Pancreatitis has been attributed to some NSAIDs and it may be a rare complication for the entire class. The case of pancreatitis described in the hospitalization section is not particularly incriminating, but it could lend some support to including pancreatitis in the probably causally related category, as the sponsor had done in the proposed labeling.

The hepatotoxicity is a significant concern with this drug. It may well be more hepatotoxic than diclofenac. The first cases of significant liver enzyme elevations developed after about a month.

The safety data base included fewer than 200 patients exposed to chronic dosing of 200 mg/day or more. Having fewer than 300 patients exposed is insufficient to support a maximum dose of 200 mg/day. Over 300 patients have been exposed to 150/day or more, so a maximum dose of 150 mg/day is supportable.

RECOMMENDATIONS:
The labeling will need special warnings about the hepatotoxic effect of bromfenac and the need to limit duration of exposure. The general NSAID class labeling for the GI warning and recent NSAID verbiage for the other warnings and precautions can be adapted for bromfenac.

The indication should be limited to the short-term management of pain. The dosage and administration section of the labeling should explicitly limit the duration of treatment with bromfenac.

The maximum daily dose should be limited to 150 mg/day. It could be raised after sufficient and satisfactory safety data are accumulated.

John E Hyde
John E. Hyde, PhD, MD

12-26-95
Peer Reviewer

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TABLE 3.8
COMBINED OA AND RA POPULATION: CUMULATIVE EXTENT OF EXPOSURE
(NUMBER [N(%)] OF PATIENTS)[a]

Study Drug Total Daily Dose	≥1 Days)	≥8 Days	≥31 Days	≥61 Days	≥91 Days	≥181 Days	≥271 Days	>360 Days
Total Bromfenac	926 (100)	902 (97)	799 (86)	638 (69)	578 (62)	474 (51)	291 (31)	193 (21)
Men <65 years	142 (100)	138 (97)	124 (87)	99 (70)	90 (63)	75 (53)	43 (30)	32 (23)
Men ≥65 years	127 (100)	125 (98)	111 (87)	86 (68)	76 (60)	65 (51)	49 (39)	31 (24)
Women <65 years	393 (100)	382 (97)	332 (84)	264 (67)	239 (61)	191 (49)	103 (26)	64 (16)
Women ≥65 years	264 (100)	257 (94)	232 (88)	189 (72)	173 (66)	143 (54)	96 (36)	66 (25)
Race								
White	792 (100)	773 (98)	687 (87)	546 (69)	494 (62)	404 (51)	242 (31)	160 (20)
Black	90 (100)	87 (97)	76 (84)	62 (69)	56 (62)	47 (52)	36 (40)	25 (28)
Other	44 (100)	42 (95)	36 (82)	30 (68)	28 (64)	23 (52)	13 (30)	8 (18)
Bromfenac 200-225 mg	197 (100)	188 (95)	164 (83)	134 (68)	124 (63)	105 (53)	37 (19)	24 (12)
Bromfenac 150-199 mg	119 (100)	114 (96)	102 (86)	92 (77)	81 (68)	68 (57)	61 (51)	50 (42)
Bromfenac 76-149 mg	516 (100)	509 (99)	453 (88)	380 (74)	349 (68)	283 (55)	178 (34)	108 (21)
Bromfenac ≤ 75 mg	94 (100)	91 (97)	80 (85)	32 (34)	24 (26)	18 (19)	15 (16)	11 (12)
Diclofenac	78 (100)	76 (97)	64 (82)	58 (74)	48 (62)	39 (50)	7 (9)	0 (0)
Ibuprofen	159 (100)	154 (97)	142 (89)	127 (80)	116 (73)	100 (63)	91 (57)	84 (53)
TOTAL PATIENTS	1163 (100)	1132 (97)	1005 (86)	823 (71)	742 (64)	613 (53)	389 (33)	277 (24)

a: Percent based on total number of patients in dose or group.

The following sections identify and provide information on patients in each of the chronic pain subpopulations who experienced a neoplasm or carcinoma. Table 5.33 presents patient information for events reported for the Combined OA and RA population. For the sake of completeness the table also includes information on patients who are part of the Short-term OA population and identifies all chronic pain subpopulations to which a patient belongs. Discussion of the other chronic pain subpopulations will include tables which identify the patient by number only. Detailed information on these patients can be obtained by referring back to the complete table in the Combined OA and RA population section.

Combined OA and RA population

Of the 26 patients identified as having had a neoplasm or carcinoma, 25 patients were in the Combined OA and RA population. The other patient, treated with naproxen, was in the Short-term OA population. All 26 patients are listed in the following table.

TABLE 5.33
CHRONIC PAIN STUDIES
NEOPLASMS AND CARCINOMAS

Treatment Patient number	Chronic Pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART (verbatim if different)	Remarks
Bromfenac 200-225 mg						
30925-002	OARA OA	F	56	192	Breast neoplasm (Mass left breast)	Infiltrating ductal carcinoma surgically removed and patient received chemotherapy.
Bromfenac 150-199 mg						
30917-011	OARA OA	F	70	377	Breast carcinoma	Study medication was stopped temporarily. Patient received radiation therapy and completed the study 2 weeks later.
30918-010	OARA OA	F	66	379	Skin benign neoplasm (wart left thumb).	Patient had cryosurgery.
30920-008	OARA OA	F	64	164	Cervical carcinoma in-situ.	Patient was hospitalized and conization of cervix and endometrial curettage were performed. Patient was discharged in satisfactory condition.

Footnotes appear at the end of the table

TABLE 5.33
CHRONIC PAIN STUDIES
NEOPLASMS AND CARCINOMAS

Treatment Patient number	Chronic Pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART (verbatim if different)	Remarks
Bromfenac 150-199 mg (continued)						
30924-038	OARA OA OA/ST	F	61	390	Breast neoplasm (lump in left breast)	A breast biopsy was done; the results were benign. Disappeared spontaneously.
30928-013	OARA OA	F	57	82	Neoplasm (colon polyps)	Present prestudy. The colon polyps were surgically removed.
Bromfenac 76-149 mg						
01804-414	OARA OA OA/ST	M	70	24	Carcinoma (prostate cancer)	Study discontinued.
30314-015	OARA OA	F	58	274	Neoplasm (fibroma)	Persisted without treatment
30315-011	OARA OA	F	56	79	Breast neoplasm (Right breast lump)	Lump disappeared after 1 day
30316022	OARA OA	F	58	204	Cervix carcinoma (positive pap smear)	Found on routine exam, follow-up with gynecologist
30317-003	OARA OA	M	65	241	Prostatic carcinoma (prostate cancer)	Found on routine exam, scheduled for radiation therapy
30318-004	OARA OA	M	69	114	Prostatic carcinoma (prostatic cancer)	Diagnosed during the study, referred for follow-up
30320-001	OARA OA	F	62	377	Uterine neoplasm (Uterine tumor)	No action taken
30321-028	OARA OA	F	51	378	Breast neoplasm (breast mass)	Mass disappeared after 1 day
30323-015	OARA OA	M	84	255	Prostatic carcinoma (prostate cancer)	Diagnosed during the study, referred for follow-up
30324-013	OARA OA	F	62	364	Breast neoplasm (left breast nodules)	Nodules persisted
30516-019	OARA RA	F	62	253	Skin benign neoplasm (warts-left elbow)	Not present prestudy. Treated with salicylic acid. Persisted.
30522-008	OARA RA	F	53	57	Neoplasm (movable, tender mass-right axilla)	Resolved spontaneously in 41 days.
30525-009	OARA RA	F	69	280	Skin benign neoplasm (dysplasia-lip lesion)	Present prestudy and worsened. Resolved in 110 days with minor surgery. Lip shaved.

Footnotes appear at the end of the table.

TABLE 5.33
CHRONIC PAIN STUDIES
NEOPLASMS AND CARCINOMAS

Treatment Patient number	Chronic Pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART (verbatim if different)	Remarks
Ibuprofen						
30922-002	OARA OA	F	70	372	Neoplasm (polyps in colon)	Present prestudy. A sigmoidoscopy revealed colon polyps. The polyps were surgically removed. Patient completed the study.
30924-022	OARA OA	M	69	59	Bladder neoplasm (bladder tumor)	Patient experienced hematuria and study medication was discontinued. He had a cystoscopy with retrograde pyelogram and a prostate biopsy. He was diagnosed with a small malignant bladder tumor which was surgically removed. Prostate biopsy was negative. He was discharged the day after surgery.
30924-034	OARA OA	F	74	365	Skin carcinoma (basal cell carcinoma R. temple)	Study medication temporarily discontinued. Carcinoma removed.
30925-008	OARA OA	F	73	381	Breast neoplasm (breast tumor)	Surgically treated.
30928-019	OARA OA	F	69	399	Breast neoplasm (left breast mass)	Patient completed Segments I and II of the study and entered the open-label extension (Segment III). The patient was withdrawn from the study 17 days later because of an earlier biopsy of the left breast that showed extensive multifocal carcinoma. The patient underwent a modified mastectomy.
30928-023	OARA OA	F	73	292	Skin benign neoplasm (3 mm pedunculated varicoid polyp)	The polyp persisted without treatment and the patient entered the open-label portion of the study.
Naproxen						
30318-007	OA/ST	M	58	61	Breast neoplasm	Breast neoplasm surgically removed.

a: Total days on therapy is the total number of days a patient took the drug therapy listed.

Overall OA population

Twenty-two (22) patients in the Overall OA population had a neoplasm or carcinoma and are listed in Table 5.34. Information on these patients can be obtained from table 5.33 in the Combined OA and RA population section.

TABLE 5.22
SINGLE- AND MULTIPLE-DOSE ANALGESIA STUDIES
ALLERGIC EVENTS

Treatment (dosage regimen) Patient Number	Sex	Age	Total Days on Therapy	COSTART Term	Remarks
Bromfenac 5 mg					
0201-062 [b]	M	75	1	Allergic Reaction	Allergic skin reaction to penicillin approximately 30 hours post-dose, treated with Benadryl, duration was 1.5 hours
Bromfenac 25 mg					
30145-096[a]	F	34	2	Pruritus, Peripheral edema, Rash	Patient discontinued study on day 2 following onset of mild itching, swelling and redness of both hands and feet, treated with diphenhydramine hydrochloride, events resolved by end of day.
30218-225	F	49	6	Generalized Edema	Edema of arm and eyelid occurred on day 1 with a duration of 19 hours, event disappeared after treatment with furosemide
Bromfenac 50 mg					
30218-110	F	62	3	Urticaria	Event present 1 day pre-study with a duration of 38 hours, treated with Calamine® lotion and Phenergan®.
30218-164	F	38	4	Generalized Edema	Pre-existing swelling of face and hands with a duration of 25 hours, disappeared without treatment.
Bromfenac 100 mg					
30632-016	F	74	1	Urticaria	Patient discontinued for hives which lasted 1 hour, disappeared without treatment
Naproxen Na					
30145-109[a]	F	29	2	Pruritus, Peripheral edema, Rash	Patient discontinued study on day 2 for onset of moderate to severe itching, swelling and rash on both arms, inner thighs and buttocks, treated with diphenhydramine hydrochloride, resolved by 9th day after study entry.
Ibuprofen 400 mg					
016-1051	F	17	1	Rash (Urticaria)	Rash on face 1 day post-dose lasting 7.5 hours, recovered without treatment
Placebo					
016-1202	F	18	1	Rash (Urticaria)	Rash on chest and back which occurred 1 hour post-dose and lasted 1.4 hours, recovered without treatment
31102-012	F	21	1	Urticaria	Small elevated hive around left antecubital space noted approximately 4 hours post-drug, resolved without treatment.

a: Event occurred in the multiple-dose section of the study; all other events occurred in single-dose studies.
b: Patient is not listed for this event in the data processing reports because the onset was greater than 24 hours post-dose.

Dysmenorrhea studies

Two (2) patients in the dysmenorrhea studies experienced allergic events during the first cycle of the crossover studies. On review, the events were both classified as seasonal allergies.

The following sections identify and provide information on patients in each of the chronic pain subpopulations who reported an allergic event. Table 5.24 presents information on the 30 patients in the chronic pain studies who reported an allergic event and identifies all chronic pain subpopulations in which a patient is included. Discussion of the other chronic pain subpopulations will include tables which identify the patient by number only.

Combined OA and RA population

Of the 30 patients in the chronic pain studies reporting an allergic event, 29 are included in the Combined OA and RA population; 21 taking bromfenac, 1 taking diclofenac and 7 taking ibuprofen. The one additional patient listed in Table 5.24 was taking aspirin and is part of the Short-term OA population only.

TABLE 5.24
CHRONIC PAIN STUDIES
ALLERGIC EVENTS

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different)	Remarks
Bromfenac 200-225 mg						
30515-006	OARA RA	F	39	248	Urticaria	Resolved after 10 days with treatment of diphenhydramine hydrochloride.
30522-019	OARA RA	F	80	246	Allergic reaction (Allergies)	Present prestudy. Treated with terfenadine and resolved.
30916-030	OARA OA	F	54	418	Urticaria (Hives)	Patient was treated with hydrocortisone. Symptoms resolved within 2 days
30918-025	OARA OA	M	62	394	Asthma	Present prestudy. Treated with terfenadine, oxymetazoline hydrochloride, and Primatene mist®.
30918-026	OARA OA	F	70	381	Asthma	Present prestudy. Treated with albuterol inhalation.

Footnotes appear at end of table.

TABLE 5.24
CHRONIC PAIN STUDIES
ALLERGIC EVENTS

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different)	Remarks
Bromfenac 150-199 mg						
30917-008[a]	OARA OA	F	55	19	Urticaria (Hives)	Resolved 3 days after the discontinuation of study medication.
30920-021	OARA OA	F	46	365	Urticaria (Hives on arms) Urticaria (Hives on legs)	Study medication was temporarily discontinued. Patient was treated with diphenhydramine. Symptoms resolved within 8 days.
30923-005	OARA OA	F	53	336	Face edema (Right eye swelling)	Treated with sulfacetamide and resolved.
Bromfenac 76-149 mg						
30313-022	OARA OA	F	58	410	Allergic reaction (Allergies)	Treated with diphenhydramine hydrochloride. Resolved within 4 days.
30314-027	OARA OA	F	68	43	Allergic reaction (allergies related to septra)	Resolved spontaneously in 8 days.
30317001	OARA OA	F	72	343	Angioedema (Angioedema of upper lip)	Resolved spontaneously after 4 days, no evidence of systemic involvement
30324-008	OARA OA	M	52	390	Urticaria	Treated with hydroxyzine and resolved.
30326-009	OARA OA OA/ST	F	68	337	Allergic reaction other than drug (Allergic reaction to an insect bite)	Event began 36 days into 303 DB while patient was on bromfenac. Treated with prednisone. Resolved within 8 days, 2 days after patient entered 303 OL.
30522-001	OARA RA	F	56	108	Face edema (facial swelling)	Resolved spontaneously.
30522-007	OARA RA	M	30	254	Urticaria (urticaria lesion (mild) R. thumb)	Present prestudy. Treated with diphenhydramine hydrochloride.
					Face edema (upper lip swelling)	Present prestudy. Treated with diphenhydramine hydrochloride and resolved.
30522-017	OARA RA	M	30	254	Allergic reaction (allergies)	Present prestudy. Treated with pseudoephedrine hydrochloride and resolved.
30522-041	OARA RA	F	63	249	Asthma	Present prestudy. Treated with chlorpheniramine maleate.
30523-010	OARA RA	F	50	57	Allergic reaction (allergies)	Present prestudy. Treated with ephedrine hydrochloride.

Footnotes appear at end of table.

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TABLE 5.24
CHRONIC PAIN STUDIES
ALLERGIC EVENTS

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different)	Remarks
Bromfenac < 75 mg						
30316-017	OARA OA OA/ST	F	60	142	Face edema (swelling in face)	Event started when patient was 29 days into 303 DB protocol. Resolved without treatment in 24 days during which the patient had entered the 303 OL protocol.
30316-030	OARA OA OA/ST	F	67	397	Face edema (L. eye-swelling & redness in peri-orbital area)	Event started on day 34 of the 303 DB protocol. Patient discontinued use of eye drops. Resolved within 8 days, when the patient was in the 303 OL protocol.
30327-028	OARA OA	F	70	67	Urticaria	Resolved spontaneously.
Diclofenac						
30521-010	OARA RA	F	43	233	Urticaria	Resolved after decreasing the dosage of methotrexate.
Ibuprofen						
30918-006	OARA OA	F	68	41	Asthma	Present prestudy. Treated with albuterol inhalation.
30918-030	OARA OA	F	65	373	Asthma	Present prestudy. Treated with salbutamol sulfate.
30920-011	OARA OA	M	60	400	Asthma	Present prestudy. Treated with Bronkaid Mist®.
30924-009	OARA OA	F	67	400	Urticaria (hives)	Present prestudy. Resolved spontaneously.
30924-039	OARA OA	F	70	61	Asthma	Present prestudy. Study medication temporarily discontinued. Treated with albuterol , theophylline, and pirbuterol acetate and resolved.
30928-006	OARA OA	M	71	2	Angioedema (Angioedema right arm)	Treated with diphenhydramine. Resolved within 7 days.
30928-023	OARA OA	F	73	392	Urticaria (hive like lesions hips) Urticaria (hive like lesions waist) Urticaria (hive like lesions knees)	All symptoms resolved spontaneously in 1 day.

Footnotes appear at end of table.

TABLE 5.24
CHRONIC PAIN STUDIES
ALLERGIC EVENTS

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different)	Remarks
Aspirin						
01805-504	OA/ST	F	57	22	Face edema (swelling of cheeks)	2 episodes. One resolve spontaneously in 13 days. The second episode resulted in study medication being discontinued for this event. It resolved within 2 days.

a: Total days on therapy is the total number of days a patient took the active medication listed.

Overall OA population

Twenty-one (21) patients in the Overall OA population reported an allergic event; 14 taking bromfenac and 7 taking ibuprofen. These patients are identified in Table 5.25. Information on these patients can be obtained from Table 5.24 in the Combined OA and RA population section.

TABLE 5.25
OVERALL OA POPULATION
NUMBER OF PATIENTS WITH AN ALLERGIC EVENT

Bromfenac								Comparator	
200-225 mg (n = 37)		150-199 mg (n = 119)		76-149 mg (n = 358)		<= 75 mg (n=88)		Ibuprofen (n = 159)	
3	30918-025 30918-026 30916-030	3	30923-005 30917-008 30920-021	5	30313-022 30314-027 30317-001 30326-009 30324-008	3	30316-017 30316-030 30327-028	7	30918-006 30918-030 30920-011 30924-039 30928-006 30924-009 30928-023

Short-term OA population

Four (4) patients in the Short-term OA population reported an allergic event; 3 taking bromfenac and 1 taking aspirin. These patients are identified in Table 5.26.

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TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
Bromfenac 200-225 mg/day						
30516-022[c]	OARA RA	M	73	253	None [Duodenal ulcer]	Patient completed the study. Hgb/Hct was 14.0/41.3 at baseline, decreased to 11.3/33.9 at week 28, but returned to WNL (12.3/37.1) by week 36. Fecal occult blood (FOB) was negative. Patient took flurbiprofen poststudy. Four days after completing study, patient was hospitalized for hematemesis, abdominal pain and tarry stools. An endoscopy revealed a duodenal ulcer. The patient was treated with ranitidine and famotidine and released.
30521-029[c,d]	OARA RA	F	73	36	Abdominal pain [Stomach ulcer]	Patient discontinued because of abdominal pain. Hgb/Hct remained WNL and FOB was negative. Endoscopy performed 5 days poststudy revealed a gastric ulcer. Treated with ranitidine and sucralfate. The patient had a history of peptic ulcer disease.
30522-023[c,d]	OARA RA	F	58	16	Abdominal pain, nausea, dizziness [Stomach ulcer]	Patient discontinued because of abdominal pain with Hgb/Hct unchanged; FOB negative. Endoscopy performed 5 days poststudy revealed two non-bleeding gastric ulcers. Treated with magaldrate, sucralfate, ranitidine, and aluminum hydroxide. There was a history of gastropathy, gastritis, and heartburn.
30523-012[d]	OARA RA	M	57	119	Stomach ulcer (pyloric stomach ulcer) [Stomach ulcer]	Patient discontinued because of a pyloric channel ulcer confirmed by endoscopy. Hgb/Hct decreased throughout the study (13.0/40.4 at baseline and 11.8/36.5 at week 12 repeat). Positive FOB at weeks 12 and 16. Patient found to be asymptomatic on ranitidine upon follow-up.
30525-029[d]	OARA RA	F	74	36	Stomach ulcer (antral gastric ulcer) [Stomach ulcer]	Patient discontinued because of a gastric ulcer confirmed by an upper GI series. Hgb/Hct was 13.8/41.1 at baseline and 12.1/36.5 at week 4 (final). History of GI discomfort. Patient continued on ranitidine treatment.
30518-016[c,d]	OARA RA	M	73	20	Anemia (Hct decreased with neg. hemoccult) [Stomach ulcer] [Esophageal ulcer]	Patient discontinued because Hgb/Hct decreased from 10.9/33.9 at baseline to 9.5/29.5 at week 2 (20 days). FOB were negative. Poststudy upper GI series revealed gastric and esophageal ulcers. Resolved with ranitidine treatment. Hgb/Hct returned to normal with iron treatment. The patient had a history of reflux.

Note: Footnotes appear at the end of the Table

TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
Bromfenac 150-199 mg/day						
30923-017[d]	OARA OA	F	79	267	Melena [Hemorrhoids/proctitis]	Patient discontinued because of melena. The episode of melena occurred after 264 days on study and resolved spontaneously within 4 days. A GI series was normal and a sigmoidoscopy performed 12 days poststudy revealed mild proctitis and small internal hemorrhoids. Hgb/Hct were unchanged throughout study; fecal occult blood test (FOB) was positive at weeks 8 and 40. The predominant and maximum dose the patient received was 150 mg daily.
30923-030[c,d]	OARA OA	F	76	210	Abdominal pain Diarrhea [Duodenal ulcer]	Patient discontinued because of severe diarrhea and abdominal pain (onset on study day 203). GI series done 4 days poststudy confirmed a duodenal ulcer. No significant changes in Hgb/Hct; FOB[b] was negative. Symptoms resolved with ranitidine treatment. The patient previously experienced dyspepsia, which resolved spontaneously. The predominant and maximum dose the patient received was 150 mg daily.
30924-015	OARA OA	F	86	380	Stomach ulcer [Stomach ulcer]	Patient completed the study but experienced 3 episodes (on days 39, 41,and 95) of stomach discomfort which lasted 12, 40, and 61 days, respectively. An upper GI endoscopy performed on study day 342 revealed a hiatal hernia, reflux esophagitis and peptic ulcer disease with an acute pyloric channel ulcer. No significant changes in Hgb/Hct; FOB was negative. Symptoms improved with ranitidine, and antacids. The predominant and maximum dose the patient received was 150 mg daily.
30927-020[d]	OARA OA	F	60	398	Duodenitis [Duodenitis/gastritis]	Patient completed the study. Patient experienced severe duodenitis and gastritis after 224 days on study. Patient was treated with antacids. The symptoms resolved within 59 days. No significant changes in Hgb/Hct; FOB was negative except at week 12. The predominant and maximum dose the patient received was 150 mg daily.

Note: Footnotes appear at the end of the Table

TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
Bromfenac 76-149 mg/day						
30317-031	OARA OA	M	68	105	Hematemesis [Inconclusive]	Hematemesis was reported while the patient was on heparin therapy following angioplasty. An endoscopy was performed which revealed scarring but no active ulcer or gastritis. Hemoglobin and hematocrit values were within normal limits throughout the study, and the patient's FOB tests were negative at all clinic visits. He was prescribed cimetidine and the event resolved after 1 day.
30317-032[d]	OARA OA	M	76	65	Gastrointestinal hemorrhage, hematemesis and melena [Duodenitis/gastritis]	Gastrointestinal hemorrhage, hematemesis and melena were reported. The patient was hospitalized. His hemoglobin values decreased from 15 g% to 12.5 g%; he was not transfused. An esophagogastroduodenoscopy revealed gastroduodenitis, but no active bleeding was seen. He was prescribed ranitidine and discharged.
30321-024	OARA OA	F	65	338	Esophageal ulcers (esophageal erosions) [Esophageal ulcer]	Esophageal ulcers (esophageal erosions) were reported on day 284. The diagnosis was made on a clinical basis only. Concurrently, the patient had also developed pneumonia and was treated with nystatin and cephalexin. She had a history of chronic esophageal erosions. Her hemoglobin and hematocrit values were within normal limits throughout the study; she had a single episode of 2+ FOB at week 4
30322-023[c,d]	OARA OA	M	77	90	Abdominal pain [Duodenal ulcer]	Study medication was discontinued because of persisting moderate to severe abdominal pain. A gastroduodenoscopy revealed a duodenal ulcer. There were no clinically significant changes in hemoglobin or hematocrit. The FOB test was negative throughout the study.
30323-001	OARA OA	F	51	386	Melena [Inconclusive]	Melena was reported on day 382 of therapy (4 days prior to final visit, month 13.5). No diagnostic tests or procedures were done. The patient's hemoglobin values had decreased from 12.5 g% at month 10.5 to 11.6 g% at month 13.5, and her hematocrit values had decreased from 36.5% at month 10.5 to 33.2% at month 13.5. FOB tests were negative at these visits. The melena resolved spontaneously within 2 days.

Note: Footnotes appear at the end of the Table

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TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
30324-007[c]	OARA OA	M	77	342	Gastrointestinal hemorrhage (hematochezia) [Hemorrhoids/proctitis]	Gastrointestinal hemorrhage (hematochezia) was reported on day 124 of therapy. The patient had an elevated hemoglobin (16.9 gm%) and hematocrit (49.9%) values on day 112 of therapy. At the next visit (day 140), the patient's hemoglobin value was within normal limits and his hematocrit values was 50.1%. FOB tests were negative at all clinic visits. The gastrointestinal hemorrhage was attributed to hemorrhoids and resolved after 3 days.
30324-017[c]	OARA OA OA/ST	M	78	443	Gastrointestinal hemorrhage (hematochezia) [Inconclusive]	Gastrointestinal hemorrhage (hematochezia) was reported on day 9. This patient had a history of gastrointestinal bleeding since 1989. A sigmoidoscopy performed in December of 1989 had revealed diverticula. A colonoscopy just prior to study entry showed no significant findings. Hemoglobin and hematocrit values remained within normal limits throughout the study, and FOB tests were negative.
30514-027[d,e]	OARA RA	M	51	2	Melena (bloody stools) [Inconclusive]	Patient discontinued because of melena. Hgb/Hct unchanged from baseline; FOB at baseline negative. Barium enema 5 days following discontinuation, was suggestive of Crohn's disease or malignancy. Small bowel follow-through and sigmoidoscopy performed 22 days following discontinuation of study medication were normal.
30525-002[d]	OARA RA	F	39	28	Duodenal ulcer [Duodenal ulcer]	Patient discontinued because of a 5-mm duodenal ulcer confirmed by an upper GI series. No significant changes in Hgb/Hct; FOB negative. History of gastritis. Symptoms resolved with ranitidine and antacid treatment.
Diclofenac 75 mg b.i.d.						
30519-011[c,d]	OARA RA	F	74	239	Lab test abnormal (decrease in Hgb & Hct) [Stomach ulcer]	Patient discontinued because of significantly decreased Hgb/Hct; 15.8/47.2 at baseline, 10.9/33.3 at week 32 and 11.5/35.4 at week 36 (final). FOB was trace at weeks 8 and 12 and 1+ at week 32. Patient was hospitalized for an acute antral ulcer and blood clot. Clot was removed and patient discharged 5 days later. Treated with cimetidine sucralfate and methotrexate. Upon follow-up patient was reported as doing well.

Note: Footnotes appear at the end of the Table

TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
30522-031	OARA RA	F	42	259	Hematemesis (vomit x1 with streaks of bright blood) [Inconclusive]	The episode of hematemesis occurred after 28 days on study drug and resolved after 1 day. This was judged by the investigator to be unrelated to study medication. The patient had a history of gastritis. Patient completed the study.
30522-032[c]	OARA RA	F	71	256	Melena (small amount of bright red blood in stool) [Acute diverticulitis]	The episode of melena occurred after 201 days on study drug and resolved after 1 day. The patient was subsequently diagnosed with acute diverticulitis which was judged unrelated to study medication. Experienced occasional decreases in Hgb/Hct; positive FOB at week 28, negative at final visit. History of gastropathy. Patient completed the study.
Ibuprofen						
30923-024[d]	OARA OA	M	72	246	Melena, Gastrointestinal hemorrhage, hematemesis [Duodenal ulcer]	Patient discontinued because of melena and GI hemorrhage. Patient noted melena and was admitted to ICU with Hgb of 6.2 and Hct of 18.8 (baseline Hgb = 15.7 and Hct = 47.5) and complaints of melena, diarrhea, vomiting and fever. FOB was negative. Patient was diagnosed with subacute bleeding. Patient was transfused and endoscopy was performed. The patient was found to have a nonbleeding superficial duodenal ulcer, superficial gastritis and a small Mallory-Weiss tear. The patient was discharged on acetaminophen, sucralfate and omeprazole. Hgb and Hct returned to within normal limits. FOB was negative except at final visit. The predominant and maximum dose the patient received was 2100 mg daily.
30925-008[d]	OARA OA	F	73	381	Hemorrhagic gastritis (antrum erosion) [Duodenitis/gastritis]	Patient discontinued because of hemorrhagic gastritis. Patient was admitted to hospital with complaints of melena. GI endoscopy revealed moderate diffuse gastritis, multiple superficial erosions in the antrum with evidence of recent bleeding. No significant changes in Hgb/Hct; FOB was negative except at week 56 (admission date to hospital). Symptoms resolved following treatment with famotidine. While hospitalized, the patient was diagnosed with a breast tumor. The biopsy was positive for adenocarcinoma; staging evaluation was negative for metastatic disease. The predominant and maximum dose the patient received was 1800 mg daily.

Note: Footnotes appear at the end of the Table

TABLE 5.14
CHRONIC PAIN STUDIES
GASTROINTESTINAL ULCERS AND BLEEDING

Treatment (dosage regimen) Patient Number	Chronic pain subpopulation	Sex	Age	Total Days on Therapy[a]	COSTART Term (verbatim if different) [Diagnosis][b]	Remarks
30926-012[d]	OARA OA	F	59	358	Duodenal ulcer [Duodenal ulcer]	Patient discontinued because of a duodenal ulcer. The patient was initially hospitalized for chest and back pain. The hospital report indicated that the patient had a long history of heartburn pain which radiated in the chest. The patient was discharged on ranitidine. After a week, the patient had an upper GI and small bowel series because of persisting abdominal pain. A sliding hiatus hernia without stricture and a duodenal ulcer were confirmed. No significant changes in Hgb/Hct; FOB was negative throughout study. Symptoms resolved with ranitidine treatment. The predominant and maximum dose the patient received was 1800 mg daily.
Naproxen 500 mg b.id.						
30319-015[d]	OA/ST	F	65	14	Peptic ulcer. [Inconclusive]	Study medication was discontinued for what the investigator termed a possible peptic ulcer. She had persistent hemoccult positive stools and a decrease in hemoglobin (11.8 g/dL) and hematocrit (34.9%) at week 2 of the study compared to 13.0 g/dL and 38.8% at baseline. According to the CRF, the patient reported no other symptoms. She was referred to a gastroenterologist for evaluation and diagnosis. According to the consultation report, the patient still had persistent hemoccult positive stool and mild epigastric discomfort. A colonoscopy was performed. No apparent source of bleeding in the colon was found. An esophagogastroduodenoscopy was recommended, but never performed. The patient was taken off all NSAIDs for one month and prescribed cimetidine. Follow-up weekly stool guaiacs were negative.

a: Total days on therapy is the total number of days a patient took the active medication listed.
b: Diagnosis in brackets refers to the category patient is counted under in Table 5.13
c: Ulcer was diagnosed poststudy and is not included in the study database.
d: Patient prematurely discontinued for PUB
e: Patient is excluded from the life-table analysis.

TABLE 5.30
COMBINED OA AND RA POPULATION
HOSPITALIZATIONS

Treatment Patient Number	Sex	Age	Total Days on Therapy[a]	Reason for Hospitalization
Bromfenac 200-225				
30514-003	M	42	21	Heart palpitations
30515-026	F	23	36	Gas, abdominal pain
30516-022[b]	M	73	253	Duodenal ulcer
30520-033	F	54	115	Left foot ulceration
30521-009	F	63	61	Total abdominal hysterectomy
30522-020	M	58	46	Left foot ulceration, skin graft surgery
30525-015	F	71	16	Ventricular tachycardia
30526-017	F	68	93	Atrial fibrillation
30528-013	M	65	30	Supraventricular tachycardia
30917-002	F	60	250	Bilateral total hip arthroplasty
30922-021	M	58	395	Reversible ischemic neurological deficit
30925-002	F	56	192	Left modified radical mastectomy secondary to breast carcinoma
Bromfenac 150-199				
30917-011	F	70	377	Left lumpectomy secondary to breast carcinoma
30919-004	F	66	100	Cellulitis of left foot
30919-015	F	78	305	Fever, chills, diarrhea, and increased left hip pain
30919-019[c]	F	57	59	Lower GI bleed due to previous surgical anastomosis

Footnotes appear at the end of the table

TABLE 5.30
COMBINED OA AND RA POPULATION
HOSPITALIZATIONS

Treatment Patient Number	Sex	Age	Total Days on Therapy[a]	Reason for Hospitalization
30920-008	F	64	164	Cervical carcinoma in-situ. Underwent conization of cervix and an endometrial curettage
30922-013	F	71	11	Shortness of breath and chest pains
30925-005	F	71	363	Sinus bradycardia and hypertension
30926-015	F	63	294	Chest discomfort, diagnosed unstable angina and arteriosclerotic heart disease
30926-020	F	81	411	Chest pain (10/2/93) and Cholecystectomy (12/3/93)
Bromfenac 76-149 mg				
30313-004	M	64	181	Psychomotor retardation
30313-017	F	66	414	Pain in right retrosternal and epigastric area
30313-023	F	76	229	Bilateral pneumothoraces resulting from motor vehicle accident
30317-031[b]	M	68	105	Myocardial infarction
30317-032[b]	M	76	65	Gastroduodenitis
30318-017	M	66	334	Keratitis and corneal ulceration
30321-010	F	61	110	Pancreatitis
30321-011	F	81	12	Incarcerated hernia
30321-019	F	64	194	Hysterectomy and bladder suspension
30322-003	M	72	279	Surgical repair of torn rotator cuff
30323-001[b]	F	51	386	Cardiac catheterization (chest pain)
30323-019	M	51	177	Aphakia with contact lens intolerance and epididymo-orchitis/sepsis
30323-021	F	50	344	Left leg pain
30323-026	F	67	53	Chest pain
30324-017[b]	M	78	400	Ureteroscopy
30324-021	F	52	406	Acute biliary pancreatitis
30514-001	M	67	26	Substernal pain
30520-006	F	44	252	Tendon surgery
30525-026	F	61	111	Fractures

Footnotes appear at the end of the table

TABLE 5.30
COMBINED OA AND RA POPULATION
HOSPITALIZATIONS

Treatment Patient Number	Sex	Age	Total Days on Therapy[a]	Reason for Hospitalization
Bromfenac < 75 mg				
01804-407	M	56	10	Myocardial infarction
30317-017	F	66	406	Anterior chest pain
30327-028	F	70	67	Chest pain secondary to angina pectoris
Diclofenac				
30518-006	M	66	62	Cardiac catheterization (chest pain)
30519-011[b]	F	74	239	Bleeding antral ulcer
30522-027	F	49	99	Vomiting, diarrhea
Ibuprofen				
30916-007	M	67	71	Right hip replacement
30916-025	F	61	403	Bilateral leg cellulitis
30917-009	M	79	230	Atrial fibrillation
30918-023	F	79	397	Bronchopneumonia
30919-014	F	51	391	Chest pain
30921-024	F	56	406	Carpal tunnel surgery-right hand
30922-005	M	40	404	Right radial head resection (8/24) and left elbow surgery (2/10)
30922-012	F	61	398	Herniated disc
30923-024[b]	M	72	289	Sub-acute GI bleed. Found to have a superficial duodenal ulcer, superficial gastritis, and a small Mallory-Weiss Tear
30924-022	M	69	56	Removal of small malignant bladder tumor
30924-035	F	73	406	Hysterectomy and oophorectomy
30925-008[b]	F	73	381	G.I. bleed, diagnosed peptic ulcer disease and Right radical mastectomy
30926-012[b]	F	59	358	Chest and back pain. After discontinuation, a GI and small bowel series revealed a sliding hiatus hernia without stricture and also a probable duodenal ulcer with edema.
30928-012	F	69	57	Severe pain, bruising and nausea resulting from a fall
30928-019	M	69	400	Left modified mastectomy because of extensive multifocal carcinoma in-situ

a Total days on therapy is total days patient took drug therapy listed.
b. Patient is listed in the section Gastrointestinal Perforations, Ulcers and Bleeding (PUBS).
c Patient had a study event of rectal hemorrhage that was not classified as a PUB.

MEDICAL OFFICER REVIEW

NDA Number: 20-535
Date Received: August 4, 1995
Date Reviewed: August 7 to December 21, 1995

Sponsor: Wyeth-Ayerst
P.O.Box 8299
Philadelphia, PA 19101
Nancy Holston, Regulatory Affairs
Phone: 610-341-2941

Drug Name: Bromfenac sodium

Drug Class: NSAID
Intended Use of Drug: Analgesia

Consumer Safety Officer: Chin Koerner
Medical Officer: Rudolph M. Widmark, M.D., Ph.D.

Background

Bromfenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. The drug was originally developed by A.H.Robins of Richmond, VA, before the company was acquired by American Home Products. Wyeth-Ayerst, which is a division of American Home Products, was assigned to develop bromfenac for marketing. Wyeth-Ayerst has decided to market bromfenac as an analgesic for acute pain and not for rheumatoid arthritis and/or osteoarthritis, though clinical trials were performed in both of these conditions for characterization of bromfenac's safety profile under chronic use. The outcome of these long-term studies may have contributed to the Sponsor's decision to limit the use of bromfenac to analgesia only, though it is not known whether this decision is final or temporary.

The Submission

[Review of laboratory data regarding liver, hematology (hemoglobin and hematocrit), and renal, only.]

- **The Studies**

  The submission contains a number of single-dose and multi-dose trials in support of the analgesic indication for bromfenac sodium. These short-term studies usually provide insufficient data to characterize the safety profile of a drug that may be used by some for the management of pain in chronic conditions such as osteoarthritis and rheumatoid arthritis. It was for this reason that the Sponsor was asked to provide us with safety data from long-term trials in osteoarthritis and rheumatoid arthritis. These were studies #303 (OA), 305 (RA) and 309 (OA), comprising over 800 patients. The duration of these trials was 52 weeks.

  For screening the laboratory data from these studies, the laboratory contingency tables were used. For *hepatic profile* ALT against AST and alkaline phosphatase against serum bilirubin; for *hematologic profile* hemoglobin against hematocrit and white cell blood count against neutrophils; for *renal profile* BUN against serum creatinine.

- **Liver Laboratory Data**

  ALT against AST: Because the normal range for enzyme determinations vary from laboratory to laboratory and very often within the same laboratory in the course of a long trial, the data were screened not by the values reported but through the normalized ratios, i.e. the multiples of the actual value in rapport to the Upper Limit of the Normal range (ULN).

	AST ratio				
ALT ratio	>0.0 to <1.2	≥1.2 to <3.0	≥3.0 to <8.0	≥8.0	TOTAL
>0.0 to <1.2	704	1	0	0	705
≥1.2 to <3.0	64	37	1	0	102
≥3.0 to <8.0	1	14	4	0	19
≥8.0	0	0	4	0	4
TOTAL	769	52	9	0	830

Since ALT (SGPT) is more liver-specific than AST (SGOT), 23 patients out of 830, or 2.8%, had medically significant elevations. Out of the 102 patients with ALT elevations between 1.2 and <3.0 times ULN, 44 (= 44.1% or 5.3% if related

to the total number of patients tested) had increases of at least 2 times (but less than 3 times) the ULN. This gives a cumulative rate of warning signals for bromfenac-induced hepatotoxic reactions to 8% in this relatively small sample of patients treated with bromfenac.

In the group of 4 patients with ALT elevations >8 times ULN, there were 3F (females) and 1M (male), one female patient had rheumatoid arthritis, the other three patients had osteoarthritis. Their ages ranged from 56 to 65. One patient received 50 mg/day of bromfenac, 2 took 100 mg/day, and one was given bromfenac 150 mg/day.

In the group of 19 patients with ALT elevations ≥3.0 to <8 times ULN, there were 14F (females) and 5M (male), 3 female patients and 1 male patient had rheumatoid arthritis, the remainder had osteoarthritis. Their ages ranged from 40 to 77. One patient received 50 mg/day of bromfenac, 3 took 100 mg/day, 8 were given bromfenac 150 mg/day, 1 got 200 mg/day, and 6 were on a variable dosage schedule.

Regarding the time of treatment with bromfenac when the ALT elevations occurred:

For those which are viewed as medically significant, i.e., >3 times ULN, they all occurred during the first 6 months of therapy. In these cases, the mean duration of treatment was 80 days, but the median was 50 days, and the first event was detected at week 4 after taking bromfenac.

For those which are viewed as signaling a possible liver problem, i.e., ALT elevations between 2 and <3 times ULN, they all occurred sporadically up to 14 months, but the majority were detected during the first three months of therapy. In these cases, the mean duration of treatment was 90 days, but the median was 53 days, and the first event was detected at 9 days after taking bromfenac.

It is interesting and important to note that the majority of patients complained about "flu-like" symptoms, usually two weeks before the ALT elevations were detected.

In a document forwarded to me by the Sponsor on December 20, 1995, in answer to our request to give us follow-up data on patients with significant ALT elevations, it appears as if patients, once discovered of having elevated ALT-values and discontinued from treatment with bromfenac, normalized, in most cases, in 1 to 2 months after discontinuation, except for patient #30518010, who was in the study for 190 days and had highly elevated ALT-values for the one month the patient was followed.

A few patients discovered with slightly elevated ALT-values, however, normalized despite continuation of treatment with bromfenac. This is not an unknown phenomenon and was seen with other NSAIDs during their IND development. What points to bromfenac as having a real "liver problem" was one patient who developed acute pancreatitis during treatment with bromfenac in one of the clinical trials: The patient, a 61-year-old female with osteoarthritis, received bromfenac 100 mg/day for 10 weeks, when she started experiencing severe epigastric distress. She was treated with Zantac, but later that day she was hospitalized with "intolerable" abdominal pain. Clinical and laboratory examination suggested acute pancreatitis. Ultrasound showed no gallstones. Although the investigator did not think that there was any relationship to bromfenac treatment, the medical monitor of the Sponsor did not exclude the possibility. [RMW: Past experience with diclofenac makes the relationship to bromfenac likely. What is different from the diclofenac experience, is that all cases of diclofenac-related acute pancreatitis were reported post-marketing, and not a single case occurred during pre-NDA clinical trials.]

The review of the "liver" laboratory data from the submission shows that bromfenac sodium causes hepato-cellular damage to a greater degree than other NSAIDs, even diclofenac. Although the repair process seems to occur in almost all cases when the drug is discontinued, it should not be forgotten that patients in clinical trials are closely monitored, which is difficult to achieve in the practice of medicine. The situation is further complicated by the tremendous interference of food on the absorption of the drug (see Pharmacokinetic Review). The lack of data pointing to drug-induced cholestatic hepatitis underlines the hepato-cellular mechanism of bromfenac-induced liver damage.

Conclusions: Bromfenac sodium does not appear to be an NSAID that could be used with relative safety in osteoarthritis and rheumatoid arthritis. Single-dose analgesic trials have shown that the drug is an effective analgesic, and could be useful in the short-term management of pain. Long-term use of bromfenac sodium seems not advisable because of its hepato-toxicity. "Flu-like" symptoms point to a beginning of hepatic adverse events around week two of bromfenac treatment.

- **Renal Laboratory Data**

There was nothing unusual seen in the contingency tables that examined BUN versus serum creatinine values in this submission.

■ **Hematological Laboratory Data**

There was nothing unusual seen in the contingency tables that examined hemoglobin versus hematocrit values in this submission.

Rudolph M. Widmark, MO 12-22-95
Date

John G Hyde 1-4-95
Peer Reviewer

APPEARS THIS WAY
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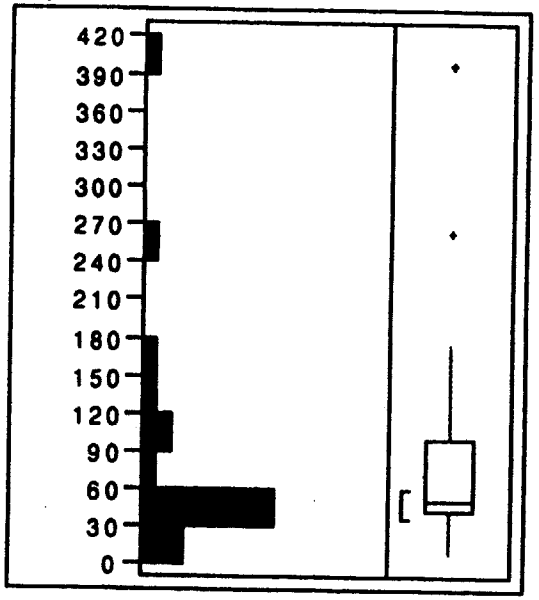
2 ≤ SGPT Ratio < 3

Day of Occurence

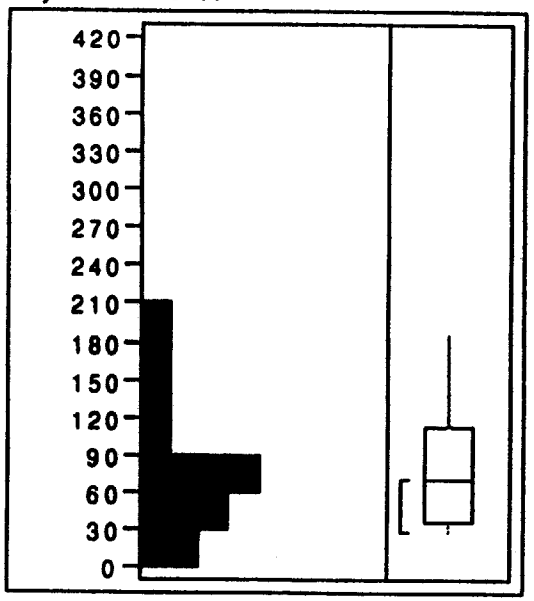


Quantiles	Percentage	Value
maximum	100.0%	399.00
	99.5%	399.00
	97.5%	399.00
	90.0%	266.00
quartile	75.0%	100.00
median	50.0%	53.00
quartile	25.0%	43.00
	10.0%	15.00
	2.5%	9.00
	0.5%	9.00
minimum	0.0%	9.00

Moments	Value
Mean	89.4737
Std Dev	96.7289
Std Err Mean	22.1911
upper 95% Mean	136.0952
lower 95% Mean	42.8521
N	19.0000
Sum Wgts	19.0000

3 ≤ SGPT Ratio

Day of Occurence



Quantiles	Percentage	Value
maximum	100.0%	185.00
	99.5%	185.00
	97.5%	185.00
	90.0%	172.60
quartile	75.0%	113.50
median	50.0%	70.00
quartile	25.0%	37.50
	10.0%	29.00
	2.5%	29.00
	0.5%	29.00
minimum	0.0%	29.00

Moments	Value
Mean	79.1538
Std Dev	50.2541
Std Err Mean	13.9380
upper 95% Mean	109.5221
lower 95% Mean	48.7856
N	13.0000
Sum Wgts	13.0000