CONFIDENTIAL: SBA Summary for Bromfenac Protocol 792-A-302-NZ

A Single-dose (Placebo-controlled) and Multiple-dose Comparison of Bromfenac Sodium (AHR-10282B) 50 and 25 mg, Naproxen Sodium 550/275 mg, and Ketorolac 30 mg in Patients with Moderate to Severe Postoperative Pain: Final Report.

IND DRUG:	Bromfenac	DOSES:	50, 25 mg oral
REFERENCE DRUGS:	Naproxen sodium Ketorolac Placebo	DOSES:	550/275 mg oral 30 mg IM
TOTAL PATIENTS ENROLLED:	218	DURATION OF DOSING:	Single dose, 12 hr Multiple dose, up to 7 days
INVESTIGATORS:	Colin R. Brown, MD, Hamilton, New Zealand John Moodie, MD, Hamilton, New Zealand		

PURPOSE: The purpose of this study was to compare the efficacy and safety of single oral doses of bromfenac, naproxen sodium, parenteral ketorolac (IM), and placebo for up to 12 hours and to compare the efficacy and safety of multiple doses of bromfenac and naproxen sodium for up to 7 days in patients with moderate to severe pain after orthopedic or gynecological surgery.

METHOD: This double-blind, parallel, inpatient study consisted of a 12-hour single-dose, placebo-controlled section and a multiple-dose section for up to 7 days. The study was performed at one site. Each patient received an initial single dose of one of five treatments: bromfenac 50 mg, bromfenac 25 mg, naproxen sodium 550 mg, ketorolac 30 mg (IM), or placebo (capsules and IM). Patients then had the option of continuing in a multiple-dose section in which they received one of three active oral dose treatments: bromfenac 50 mg, bromfenac 25 mg, and naproxen sodium 275 mg. In the single-dose section, patient assessments of pain intensity, pain relief, pain half-gone, and time to meaningful pain relief were recorded for up to 12 hours; global assessments were also recorded. In the multiple-dose section, patient assessments of pain intensity at 0 and 2 hours after the first dose were recorded in addition to daily global assessments.

RESULTS: Efficacy was analyzed for the total population (n=214 with any postbaseline data) and two subpopulations, using intent-to-treat (ITT) and valid-for-efficacy (VFE) analyses. The orthopedic surgery subpopulation included those patients who underwent orthopedic (n=106) or thoracic (removal of a rib, n=1) surgery. The gynecological surgery subpopulation included those patients who underwent gynecological surgery (n=105) or other abdominal surgery (n=2). The results for the ITT total population are shown in Figures 1-4 and Tables 1-6. The results of the ITT analyses for all populations are described below. The results of the VFE analysis were similar to the ITT analysis.

The single-dose analysis of data from the total population showed bromfenac 50 mg, naproxen sodium, and ketorolac to be significantly superior to placebo for the following primary variables: 3-hour and final TOPAR, final SPID, and 3-hour and final SPRID. Bromfenac 25 mg was superior to placebo for the final summed scores. Analysis of the pain relief, PID, and PRID hourly variables showed all active treatments to be significantly better than placebo starting at hour 2. The only significant difference between any active treatments was noted at hour 6 when bromfenac 50 mg was superior to naproxen sodium in all 3 variables and to ketorolac in PID. The last period with an overall significant difference among treatments was hour 8 for pain relief and PRID and hour 7 for PID, with bromfenac 50 mg the only treatment still superior to placebo. The results are confounded by an unusually large placebo response in the first 2 hours.

Analysis of the orthopedic surgery subpopulation revealed no significant differences among treatments for any of the variables examined. The numerical trend favored bromfenac 50 mg and naproxen sodium over the other treatments in this subpopulation. The results of the analysis of the gynecological surgery subpopulation were similar to those obtained with the total population.

The pain half-gone and global assessments for the total population showed bromfenac, naproxen sodium, and ketorolac all to be superior to placebo. Pain half-gone and global assessments for the gynecological surgery subpopulation gave similar results. There were no significant differences between the treatment groups in the numbers of patients reporting meaningful relief or in the survival analysis of time to meaningful relief. Among those who reported meaningful relief, the mean time to meaningful relief was generally similar for all treatments.

In the orthopedic surgery subpopulation, the treatment effect was investigated separately for the fed and fasted populations (no other analyses were warranted since there were only two fed patients in the gynecological surgery subpopulation). The most pronounced difference was observed in the bromfenac 50 mg group, with a considerably greater response found in fed patients. Differences in the other groups were relatively small, with bromfenac 25 mg and ketorolac showing slightly better responses in fed patients compared to fasted patients, whereas naproxen sodium and placebo gave slightly worse responses in fed patients.

CONFIDENTIAL: BROMFENAC 792-A-302-NZ (Total Population)

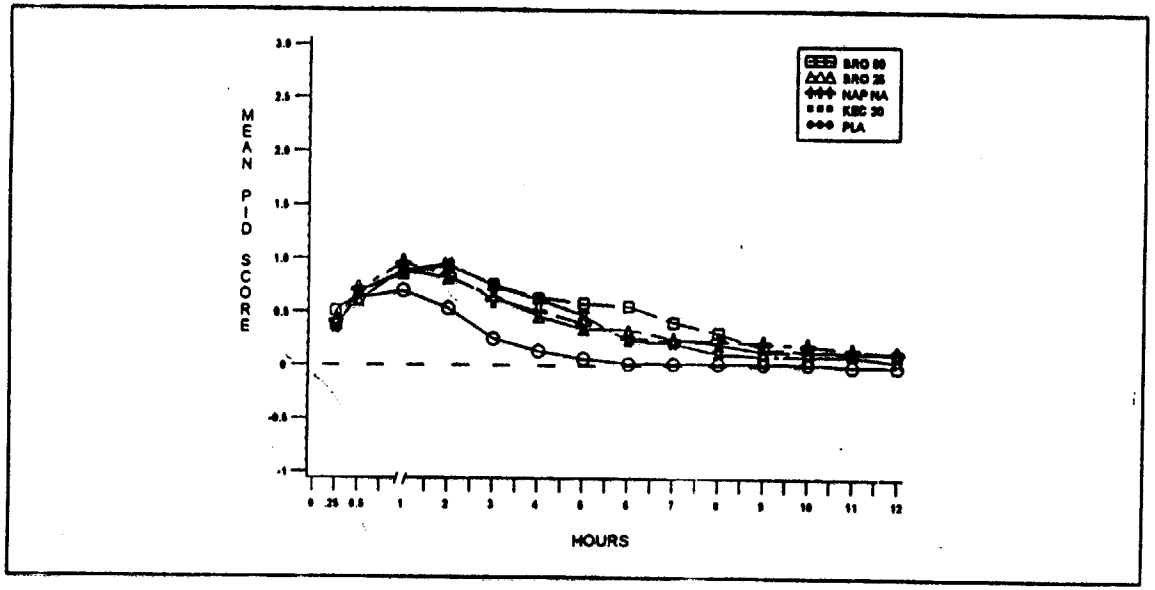
There were no significant differences observed between the two bromfenac doses and naproxen sodium in the analysis of the multiple-dose section.

In the single-dose section, one or more TESE were reported for 8 patients who were treated with bromfenac 50 mg, 4 patients who were treated with bromfenac 25 mg, 7 patients who were treated with naproxen sodium, 6 patients who were treated with ketorolac IM, and 8 patients who were treated with placebo. In the multiple-dose section, one or more TESE were reported for 24 patients treated with bromfenac 50 mg, 15 patients treated with bromfenac 25 mg, and 11 patients treated with naproxen sodium. In the multiple-dose section, there were significant differences among treatment groups in the COSTART categories Any Study Event, Body as a Whole (both favoring naproxen sodium), and diarrhea (occurred only in the naproxen sodium group). The rates of safety-related withdrawals were comparable among treatment groups.

CONCLUSIONS: The results of this study indicate that single doses of bromfenac are at least as effective as naproxen sodium and ketorolac in the relief of postoperative pain. Multiple doses of bromfenac were as effective as naproxen sodium.

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]

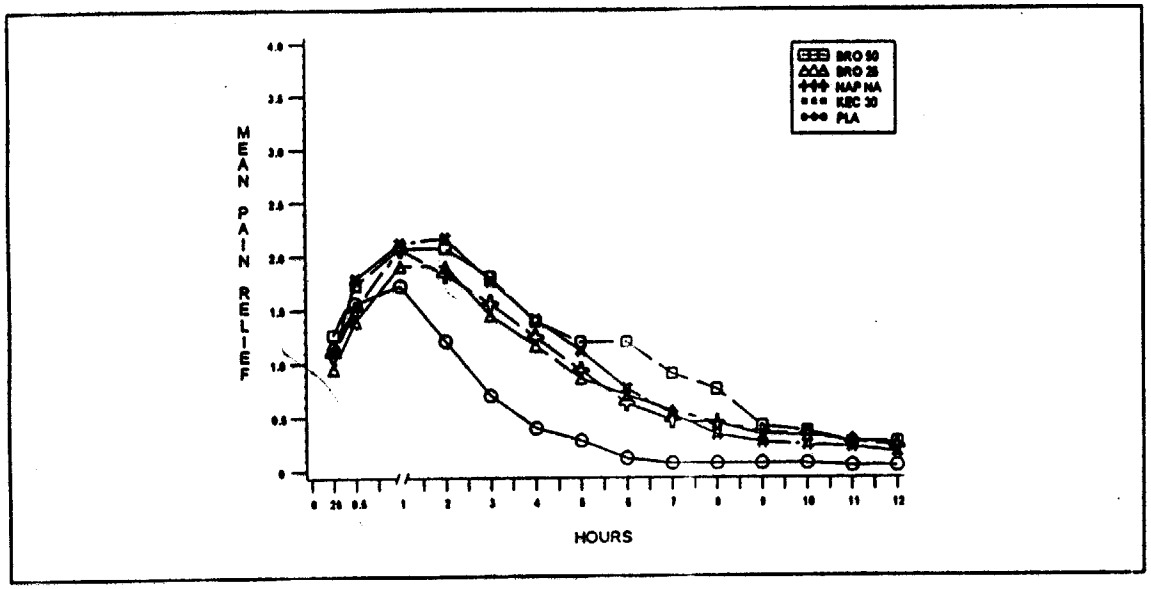
Treatment Group	n	3-hour SPID	Final SPID	Peak PID
Bromfenac 50 mg	41	2.33	5.72A	1.22
Bromfenac 25 mg	43	2.13	4.56A	1.16
Naproxen Na 550 mg	45	2.24	4.87A	1.29
Ketorolac 30 mg IM	42	2.33	4.68A	1.10
Placebo	43	1.51	1.97B	0.98
p-value		0.0967	0.0160	0.3243
Root MSE		1.6358	5.2054	0.7063

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	0.51(0.55) 41 (a)	0.68(0.65) 41	0.85(0.69) 41	0.93(0.82) 33	0.76(0.86) 27 A (d)	0.63(0.86) 21 A	0.59(0.84) 16 A	0.56(0.84) 14 A	0.41(0.71) 13 A	0.32(0.61) 11	0.17(0.50) 6	0.15(0.48) 5	0.12(0.46) 3	0.12(0.46) 3
Bromfenac 25 mg	0.42(0.54) 43	0.60(0.73) 42	0.88(0.76) 40	0.81(0.85) 30	0.65(0.87) 22 A	0.47(0.77) 16 A	0.35(0.72) 13 AB	0.35(0.72) 7 AB	0.26(0.58) 7 AB	0.21(0.51) 6	0.14(0.47) 3	0.14(0.47) 3	0.14(0.47) 2	0.12(0.45) 2
Naproxen Na550 mg	0.42(0.54) 45	0.71(0.51) 45	0.96(0.56) 45	0.84(0.74) 36	0.62(0.89) 29 A	0.51(0.84) 20 A	0.40(0.72) 15 A	0.27(0.65) 11 BC	0.24(0.71) 6 AB	0.24(0.71) 5	0.22(0.67) 4	0.20(0.66) 4	0.16(0.52) 3	0.13(0.50) 2
Ketorolac 30 mg IM	0.36(0.48) 42	0.69(0.60) 42	0.88(0.55) 42	0.95(0.76) 36	0.74(0.86) 30 A	0.62(0.76) 22 A	0.48(0.67) 20 A	0.24(0.58) 15 BC	0.21(0.52) 9 AB	0.12(0.40) 6	0.10(0.37) 4	0.10(0.37) 3	0.10(0.37) 2	0.05(0.22) 2
Placebo	0.37(0.54) 43	0.63(0.79) 40	0.70(0.86) 40	0.53(0.77) 27	0.26(0.44) 17 B	0.14(0.35) 8 B	0.07(0.26) 6 B	0.02(0.15) 4 C	0.02(0.15) 1 B	0.02(0.15) 1	0.02(0.15) 1	0.02(0.15) 1	0.00(0.00) 1	0.00(0.00) 1
p-value Trt (b)	0.744	0.832	0.445	0.083	0.023	0.014	0.007	0.004	0.043	0.096	0.409	0.540	0.466	0.436
p-value Trt*Surgery (b)	0.493	0.165	0.473	0.327	0.063	0.207	0.609	0.648	0.229	0.145	0.493	0.646	0.819	0.901
p-value Trt*Baseline (c)	0.379	0.772	0.297	0.140	0.131	0.135	0.124	0.268	0.295	0.272	0.521	0.449	0.603	0.447
Root MSE (b)	0.530	0.630	0.658	0.771	0.783	0.735	0.670	0.633	0.571	0.514	0.468	0.462	0.414	0.382

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + S(k) + TS(ik) + error
(c) Model: PID = 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 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	41	5.50A	13.02A	2.68
Bromfenac 25 mg	43	4.82AB	10.32A	2.47
Naproxen Na 550 mg	45	4.99A	10.54A	2.62
Ketorolac 30 mg IM	42	5.58A	11.40A	2.55
Placebo	43	3.72B	5.21B	2.07
p-value		0.0409	0.0060	0.1332
Root MSE		3.0802	9.9538	1.2034

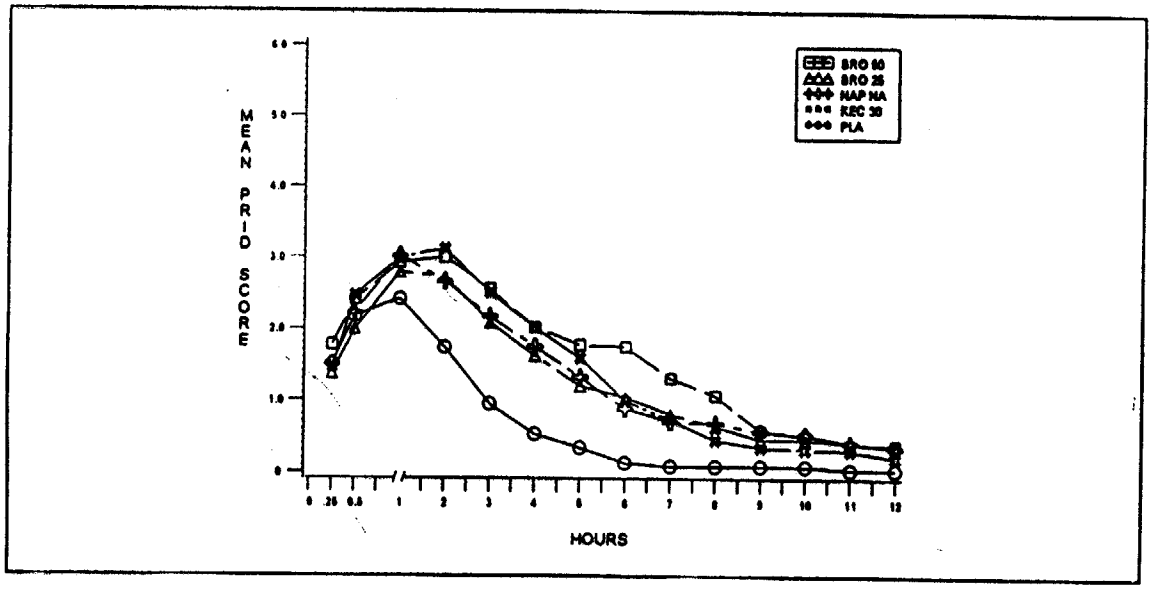
a For a given variable, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, the means 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	1.27 (0.95) 41 (a)	1.73 (1.12) 41	2.07 (1.08) 41	2.07 (1.46) 33 A (d)	1.80 (1.57) 27 A	1.39 (1.58) 21 A	1.20 (1.65) 16 A	1.20 (1.65) 14 A	0.90 (1.43) 13 A	0.76 (1.28) 11 A	0.41 (1.02) 6	0.37 (0.97) 5	0.27 (0.90) 3	0.27 (0.90 3
Bromfenac 25 mg	0.95 (0.95) 43	1.40 (1.28) 42	1.91 (1.27) 40	1.91 (1.60) 30 A	1.44 (1.61) 22 A	1.16 (1.56) 16 A	0.86 (1.41) 13 AB	0.70 (1.37) 7 AB	0.56 (1.18) 7 AB	0.44 (0.98) 6 AB	0.33 (0.92) 3	0.33 (0.92) 3	0.28 (0.85) 2	0.26 (0.82 2
Naproxen Na550 mg	1.09 (0.97) 45	1.51 (0.92) 45	2.07 (1.07) 45	1.82 (1.39) 36 A	1.56 (1.55) 29 A	1.24 (1.57) 20 A	0.93 (1.47) 15 A	0.62 (1.25) 11 BC	0.47 (1.20) 6 AB	0.44 (1.20) 5 AB	0.36 (1.07) 4	0.33 (1.04) 4	0.27 (0.91) 3	0.22 (0.88 2
Ketorolac 30 mg IM	1.10 (1.05) 42	1.79 (1.18) 42	2.12 (1.04) 42	2.17 (1.38) 36 A	1.76 (1.53) 30 A	1.40 (1.48) 22 A	1.12 (1.33) 20 A	0.76 (1.19) 15 AB	0.52 (1.13) 9 AB	0.33 (0.90) 6 AB	0.26 (0.83) 4	0.24 (0.82) 3	0.21 (0.81) 2	0.17 (0.62 2
Placebo	1.14 (1.08) 43	1.56 (1.14) 40	1.72 (1.35) 40	1.21 (1.41) 27 B	0.70 (1.01) 17 B	0.40 (0.95) 8 B	0.28 (0.73) 6 B	0.12 (0.39) 4 C	0 07 (0.34) 1 B	0.07 (0.34) 1. B	0.07 (0 34) 1	0.07 (0 34) 1	0.05 (0.21) 1	0.05 (0.21 1
p-value Trt (b)	0.719	0.460	0.455	0.020	0.003	0.006	0.016	0.003	0.020	0.039	0.446	0.539	0 653	0.648
p-value Trt*Surgery (b)	0.142	0.704	0.650	0.493	0.119	0.270	0.504	0.751	0.577	0.517	0.558	0.706	0.864	0.933
p-value Trt*Baseline (c)	0.813	0.540	0.358	0.343	0.123	0.405	0.611	0.681	0.672	0.735	0.728	0.677	0.792	0.736
Root MSE (b)	0.994	1.106	1.159	1.422	1.437	1.423	1.337	1.240	1.122	1.001	0.882	0.864	0.792	0.739

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + S(k) + TS(ik) + error
(c) Model: PR = 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 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

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	2.41	1.69	41	12	10-16
Bromfenac 25 mg	2.02	1.93	42	15	11-21
Naproxen Na 550 mg	2.22	1.29	45	14	11-16
Ketorolac 30 mg IM	2.48	1.71	42	12	10-15
Placebo	2.33	1.83	40	13	10-17

a Raw unadjusted mean of (unextrapolated) PRID scores.

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CONFIDENTIAL: BROMFENAC 792-A-302-NZ (Total Population)

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

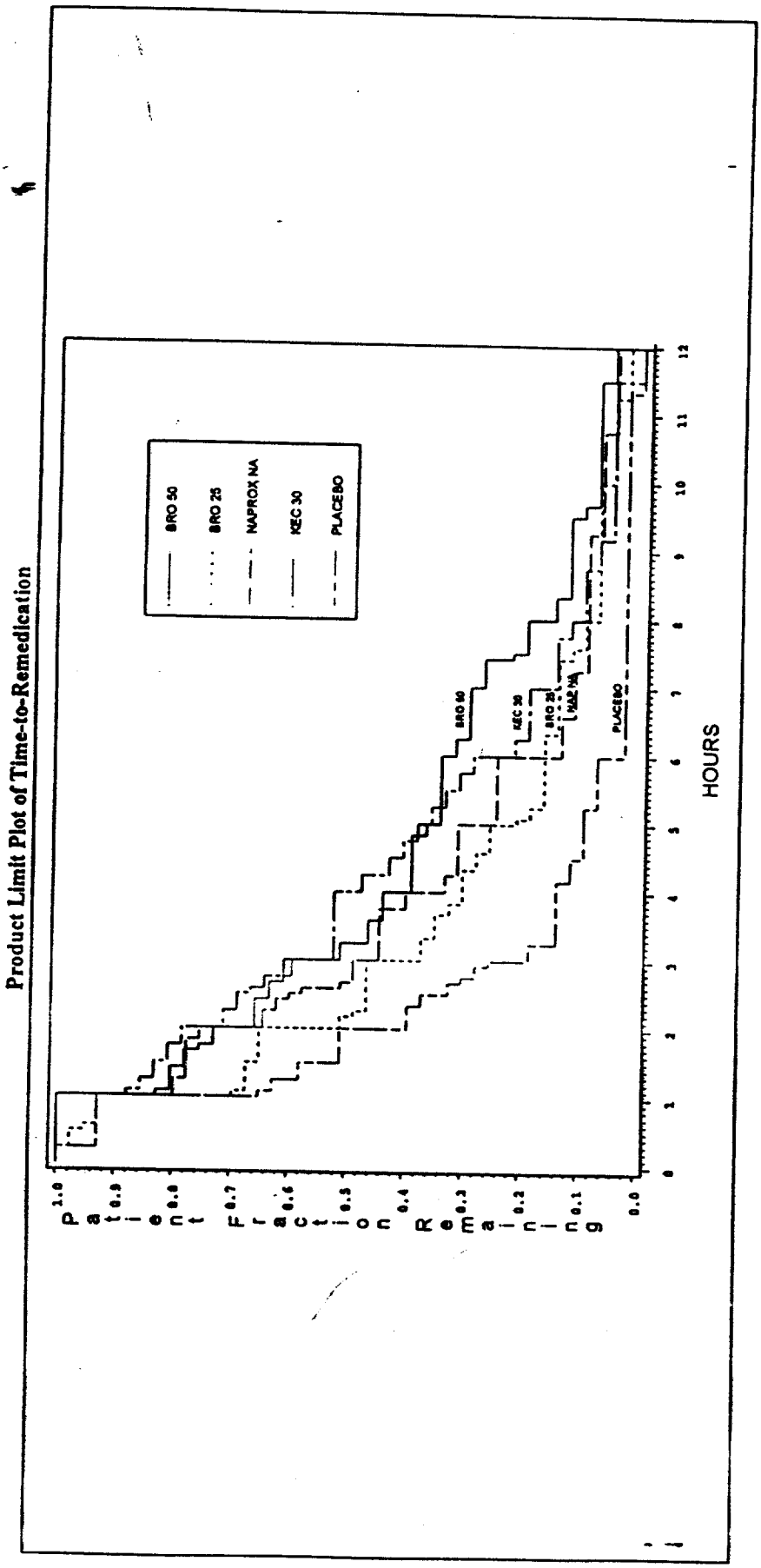


Table 5. Duration of Pain Relief (dur-PR)

Treatment Group	n	Calculated Time to Remedication	
		Mean [a] h:min	95% CI [b] h:min
Bromfenac 50 mg	41	4:38 (A) [c]	(3:33, 5:44)
Brofenac 25 mg	43	3:43 (A)	(2:43, 4:42)
Naproxen Na 550 mg	45	4:02 (A)	(3:07, 4:57)
Ketorolac 30 mg IM	42	4:21 (A)	(3:28, 5:14)
Placebo mg	43	2:28 (B)	(1:50, 3:05)

(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	1:45 (1:00, 3:00)	3:15 (2:25, 6:00)	7:25 (4:00, 8:20)
Bromfenac 25 mg	1:00 (1:00, 2:00)	3:00 (2:00, 3:50)	5:05 (3:20, 7:35)
Naproxen Na 550 mg	2:00 (1:00, 2:35)	3:00 (2:25, 4:00)	6:00 (4:00, 6:00)
Ketorolac 30 mg IM	2:00 (1:15, 2:45)	4:00 (2:35, 5:15)	6:00 (4:45, 7:00)
Placebo	1:00 (1:00, 1:30)	2:00 (1:15, 2:30)	3:00 (2:20, 4:10)

CONFIDENTIAL: SBA Summary for Bromfenac Protocol 792-A-306-US

A Single-dose (Placebo-controlled) and Multiple-dose Comparison of Bromfenac Sodium (AHR-10282b) 100 and 50 mg, Acetaminophen 650 mg/oxycodone 10 mg, and Ibuprofen 400 mg in Patients with Moderate to Severe Postoperative Pain: Final Report.

IND DRUG:	Bromfenac (BRO)	DOSES:	100, 50 mg oral
REFERENCE DRUGS:	Acetaminophen/ Oxycodone (APOX)	DOSES:	650/10 mg oral
	Ibuprofen (IBU)		400 mg oral
	Placebo		
TOTAL PATIENTS ENROLLED	238	DURATION OF DOSING	Single dose, 8 hr. Multiple dose, up to 5 days
INVESTIGATORS:	Gary Johnson, MD; J. Dallas Van Wagoner, MD, Salt Lake City, Utah, USA; Stephen A. Cooper, DMD, PhD, Philadelphia, PA, USA		

PURPOSE: The purpose of this study was to compare the efficacy and safety of single oral doses of bromfenac, acetaminophen with oxycodone (APOX), ibuprofen, and placebo for up to 8 hours and to compare the efficacy and safety of multiple doses of bromfenac, APOX, and ibuprofen for up to 5 days in patients with moderate to severe pain after gynecological surgery or Caesarean section.

METHOD: This double-blind, parallel, inpatient study consisted of an 8-hour single-dose, placebo-controlled section and a multiple-dose section for up to 5 days. The study was conducted by three investigators. Each patient received an initial single dose of one of five treatments: bromfenac 100 mg, bromfenac 50 mg, APOX 650/10 mg, ibuprofen 400 mg, or placebo. Patients then had the option of continuing in a multiple-dose section in which they received one of four active oral dose treatments: bromfenac 100 mg, bromfenac 50 mg, APOX 650/10 mg, and ibuprofen 400 mg. In the single-dose section, patient assessments of pain intensity, pain relief, pain half-gone, and time to meaningful pain relief were recorded for up to 8 hours; global assessments were also recorded. In the multiple-dose section, patient assessments of pain intensity at 0 and 2 hours after the first daily dose were recorded in addition to daily global assessments. Time of meals was recorded.

RESULTS: The results of the single-dose section of the study showed both bromfenac 100 mg and 50 mg to be significantly better than ibuprofen and placebo for all primary and corresponding peak variables except the peak pain relief for which both bromfenac doses were significantly better than ibuprofen, but only the 100 mg dose was significantly better than placebo. In addition, bromfenac 100 mg was significantly better than APOX for the final TOPAR, final SPID, and final SPRID variables, and bromfenac 50 mg was significantly better than APOX for the latter two variables. Analysis of the pain relief, PID, and PRID hourly assessments showed bromfenac 100 mg to be significantly better than APOX, ibuprofen, and placebo at hours 3 through 8 for all three variables. Bromfenac 50 mg was significantly better than APOX, ibuprofen, and placebo at hours 4 through 7 for PID and PRID and at hours 5 through 8 for pain relief. Of the active treatments, only the two bromfenac doses were consistently superior to placebo from hour 2 through hour 8.

The treatments showed generally similar times for onset to pain relief (on-PR) results, with all in the range of 9 to 14 minutes. There were no statistical differences found among the treatments for the directly estimated time to meaningful pain relief. Both bromfenac treatments had longer durations of pain relief than the remaining treatments. Both bromfenac treatments were superior to ibuprofen and placebo for the pain half-gone assessment; bromfenac 100 mg was also superior to APOX for this assessment. Results of the global assessment showed both bromfenac doses to be superior to ibuprofen and placebo. Food did not appear to inhibit the analgesic response.

In the multiple-dose analysis, the assessments of efficacy did not show any statistically significant differences among the treatment groups, except that the APOX group had significantly more pain at hour 0 (baseline) on Day 2 than the other treatment groups.

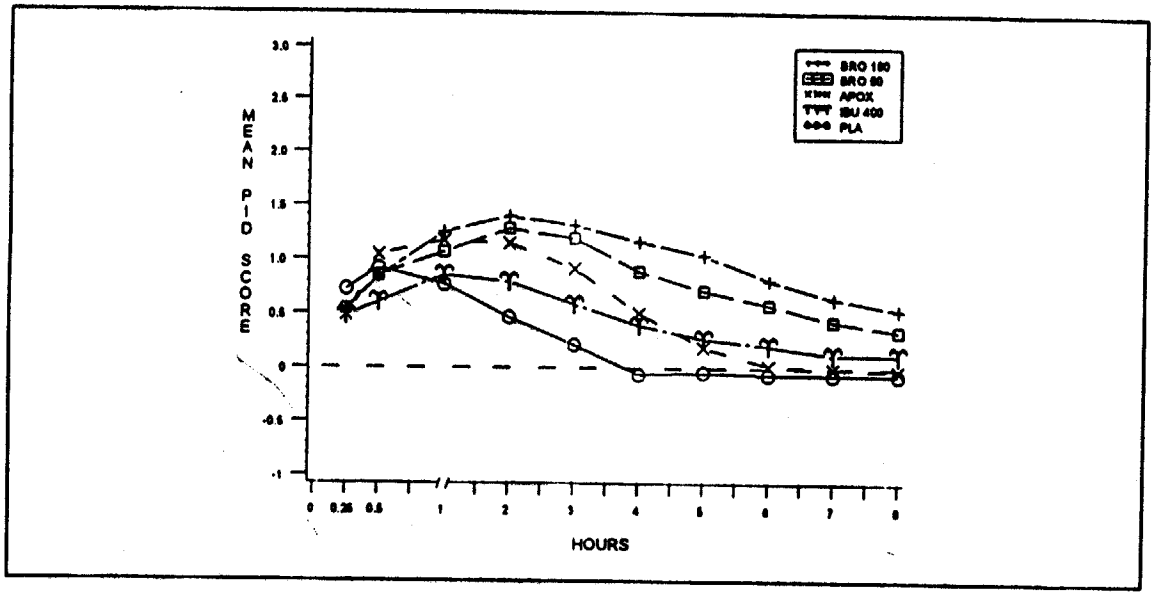
In the single-dose section, one or more TESE were reported for 18 patients (37.5%) who were treated with bromfenac 100 mg, 8 patients (17.0%) who were treated with bromfenac 50 mg, 16 patients (34.0%) who were treated with APOX, 12 patients (25.0%) who were treated with ibuprofen, and 8 patients (16.7%) who were treated with placebo. In the multiple-dose section, one or more TESE were reported for 12 patients (29.3%) who were treated with bromfenac 100 mg, 21 patients (27.3%) who were treated with bromfenac 50 mg, 16 patients (37.2%) who were treated with APOX, and 10 patients (23.3%) who were treated with ibuprofen. In the single-dose section, the bromfenac 50 mg and placebo groups had significantly fewer reports for the Nervous System and Somnolence categories than the APOX group. In the multiple-dose section, significant differences among treatment groups were observed for the COSTART categories Diarrhea (present only in bromfenac 100 mg group), Vomiting (present only in the APOX group), and Nervous System (present in the bromfenac 100 mg and APOX groups). The bromfenac 50 mg group had significantly fewer events of vomiting compared to APOX and significantly fewer events in the Nervous System category compared to bromfenac 100 mg and APOX. Because of the small numbers and many empty cells, the clinical significance of these findings is doubtful.

In the single-dose section, 15 patients withdrew from the study because of study events; 3 patients who were treated with bromfenac 100 mg, 1 patient who was treated with bromfenac 50 mg, 3 patients who were treated with APOX, 3 patients who were treated with ibuprofen, and 5 patients who were treated with placebo. In the multiple-dose segment, 24 patients withdrew because of study events; 4 patients who were treated with bromfenac 100 mg, 7 patients who were treated with bromfenac 50 mg, 10 patients who were treated with APOX, and 3 patients who were treated with ibuprofen.

CONCLUSION: The results of this study indicate that single doses of bromfenac are superior to ibuprofen and placebo. However, ibuprofen did not achieve statistical superiority over placebo in any primary variable. Relative to APOX, the tested bromfenac doses produced equivalent analgesic activity, but provided a longer duration of action. Multiple doses of bromfenac were at least as effective as ibuprofen and APOX.

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 100 mg	48	3.43A	8.21A	1.56A
Bromfenac 50 mg	46	3.13A	6.93A	1.48A
APOX 650/10 mg	47	3.00A	4.67B	1.47A
Ibuprofen 400 mg	48	2.07B	3.89BC	1.10B
Placebo	47	1.67B	2.09C	1.11B
p-value		0.0001	0.0001	0.0049
Root MSE		2.0127	4.8655	0.7936

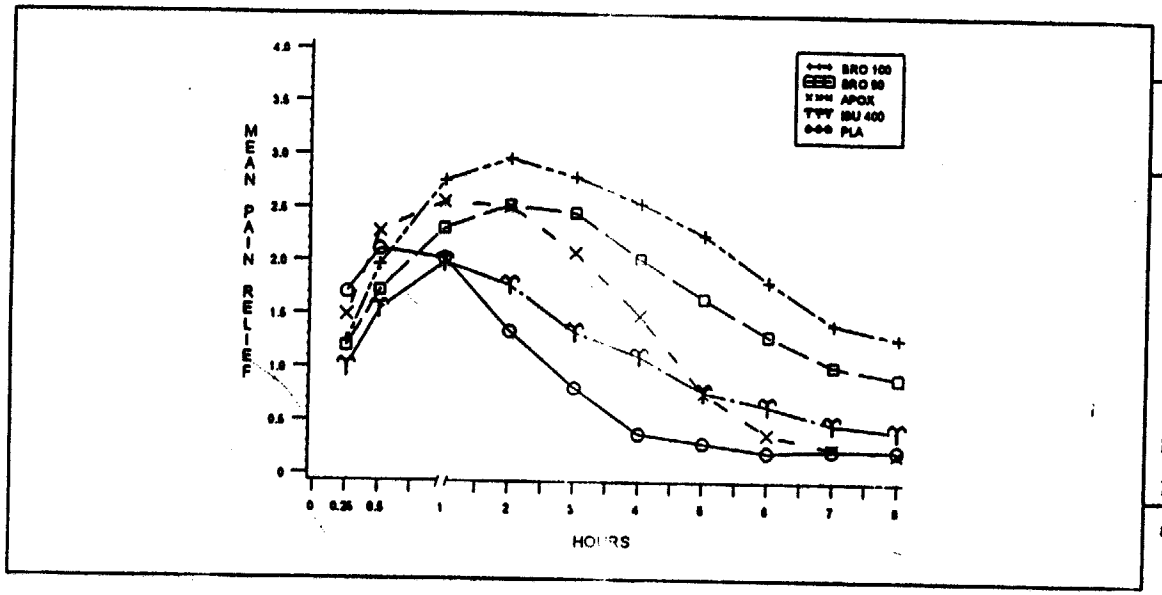
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance. When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, 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)															
	1/4		1/2		1		2		3		4		5		6		7		8	
Bromfenac 100 mg	0.52	(0.58)	0.83	(0.66)	1.25	(0.81)	1.40	(0.87)	1.31	(0.90)	1.17	(1.06)	1.04	(1.07)	0.81	(1.02)	0.65	(0.96)	0.54	(0.92)
	48 (a)		48		48	A (d)	42	A	42	A	39	A	30	A	25	A	21	A	20	A
Bromfenac 50 mg	0.54	(0.69)	0.85	(0.87)	1.07	(1.02)	1.28	(0.96)	1.20	(0.96)	0.89	(1.10)	0.72	(1.05)	0.59	(1.00)	0.43	(0.93)	0.35	(0.92)
	46		46		46	ABC	35	A	34	AB	30	A	23	A	20	A	15	A	13	AB
APOX 650/10 mg	0.49	(0.62)	1.04	(0.83)	1.17	(0.96)	1.15	(0.88)	0.91	(1.00)	0.51	(1.02)	0.19	(0.92)	0.02	(0.71)	0.00	(0.69)	-0.02	(0.68)
	47		47		47	AB	38	A	33	BC	28	B	18	B	8	B	4	B	2	C
Ibuprofen 400 mg	0.48	(0.65)	0.60	(0.76)	0.85	(0.92)	0.79	(0.90)	0.58	(0.94)	0.40	(0.98)	0.27	(0.92)	0.21	(0.87)	0.13	(0.82)	0.13	(0.82)
	47		48		48	BC	34	B	26	C	18	B	12	B	8	B	5	B	3	BC
Placebo	0.72	(0.68)	0.91	(0.75)	0.77	(0.76)	0.47	(0.72)	0.21	(0.66)	-0.06	(0.48)	-0.04	(0.55)	-0.06	(0.48)	-0.06	(0.48)	-0.06	(0.48)
	47		47		46	C	32	B	20	D	10	C	2	B	1	B	1	B	1	C
Treatment P-values (b)	0.334		0.079		0.027		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-values (c)	0.846		0.571		0.989		0.182		0.081		0.260		0.336		0.056		0.002		<0.001	
Trt*Invest P-values (c)	0.439		0.675		0.165		0.119		0.330		0.469		0.501		0.683		0.552		0.544	
Root MSE (b)	0.621		0.737		0.862		0.845		0.875		0.912		0.894		0.816		0.761		0.741	

(a) Sample sizes, not extrapolated
(b) Model: PID = u + T(i) + B(j) + I(k) + error
(c) Model: PID = u + T(i) + B(j) + I(k) + TB(ij) + TI (ik) + error
(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 100 mg	48	7.46A	17.53A	3.19A
Bromfenac 50 mg	46	6.42A	14.11AB	2.91AB
APOX 650/10 mg	47	6.69A	10.74BC	3.09A
Ibuprofen 400 mg	48	4.75B	8.62CD	2.38C
Placebo	47	4.48B	6.13D	2.45BC
p-value		0.0001	0.0001	0.0039
Root MSE		3.5414	8.8425	1.2918

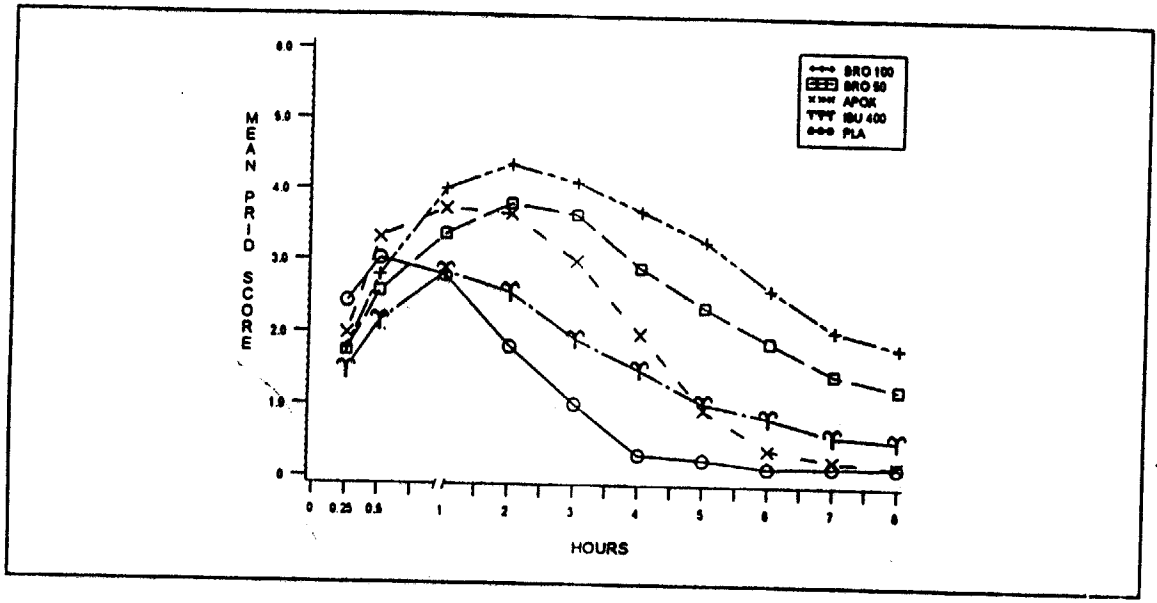
a For a given variable at each hour, means not followed by the same letter are significantly different at the 0.05 level of significance When significant treatment differences ($p<0.05$) were indicated by results of the F-test, pairwise t-tests were computed using adjusted (least-square) means. However, 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	1.25 48	(1.02) BC	1.96 48	(1.17)	2.75 48	(1.30) A	2.96 42	(1.32) A	2.79 42	(1.40) A	2.54 39	(1.60) A	2.25 30	(1.78) A	1.81 25	(1.75) A	1.42 21	(1.66) A	1.29 20	(1.57) A
Bromfenac 50 mg	1.20 46	(1.19) BC	1.72 46	(1.46)	2.30 46	(1.52) ABC	2.52 35	(1.63) A	2.46 34	(1.63) AB	2.02 30	(1.74) AB	1.65 23	(1.79) A	1.30 20	(1.70) A	1.02 15	(1.63) A	0.91 13	(1.59) A
APOX 650/10 mg	1.49 47	(1.10) AB	2.28 47	(1.36)	2.55 47	(1.36) AB	2.51 38	(1.52) A	2.09 33	(1.65) B	1.49 28	(1.53) BC	0.77 18	(1.34) B	0.38 8	(0.95) B	0.26 4	(0.82) B	0.21 2	(0.78) B
Ibuprofen 400 mg	0.99 47	(1.07) C	1.54 48	(1.25)	1.98 48	(1.42) C	1.77 34	(1.59) B	1.33 26	(1.63) C	1.10 18	(1.53) C	0.77 12	(1.42) B	0.65 8	(1.34) B	0.48 5	(1.18) B	0.42 5	(1.16) B
Placebo	1.70 47	(1.21) A	2.11 47	(1.27)	2.02 46	(1.28) BC	1.34 32	(1.37) B	0.81 20	(1.31) C	0.38 10	(0.87) D	0.30 2	(0.91) B	0.21 1	(0.72) B	0.23 1	(0.79) B	0.23 1	(0.79) B
Treatment P-values (b)	0.026		0.057		0.026		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Trt*Baseline P-values (c)	0.813		0.253		0.997		0.719		0.339		0.498		0.746		0.152		0.028		0.024	
Trt*Invest P-values (c)	0.135		0.693		0.311		0.792		0.815		0.794		0.725		0.818		0.621		0.526	
Root MSE (b)	1.114		1.303		1.378		1.479		1.524		1.482		1.484		1.341		1.253		1.203	

(a) Sample sizes, not extrapolated
(b) Model: PR = u + T(i) + B(j) + I(k) + error
(c) Model: PR = u + T(i) + B(j) + I(k) + TB(ij) + TI (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 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	(2.50) 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		0.992		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

APPEARS THIS WAY
ON ORIGINAL

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

Treatment	PRID at 30 min			Estimated on-PR	
	Mean[a]	SD	N	Time in min	95%-CI in min
Bromfenac 100 mg	2.79	1.73	48	11	9 - 13
Bromfenac 50 mg	2.57	2.27	46	12	9 - 16
APOX 650/10 mg	3.32	2.13	47	9	8 - 11
Ibuprofen 400 mg	2.15	1.95	48	14	11 - 19
Placebo	3.02	1.95	47	10	8 - 12

(a) Raw unadjusted means of (unextrapolated) PRID scores.

APPEARS THIS WAY
ON ORIGINAL

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

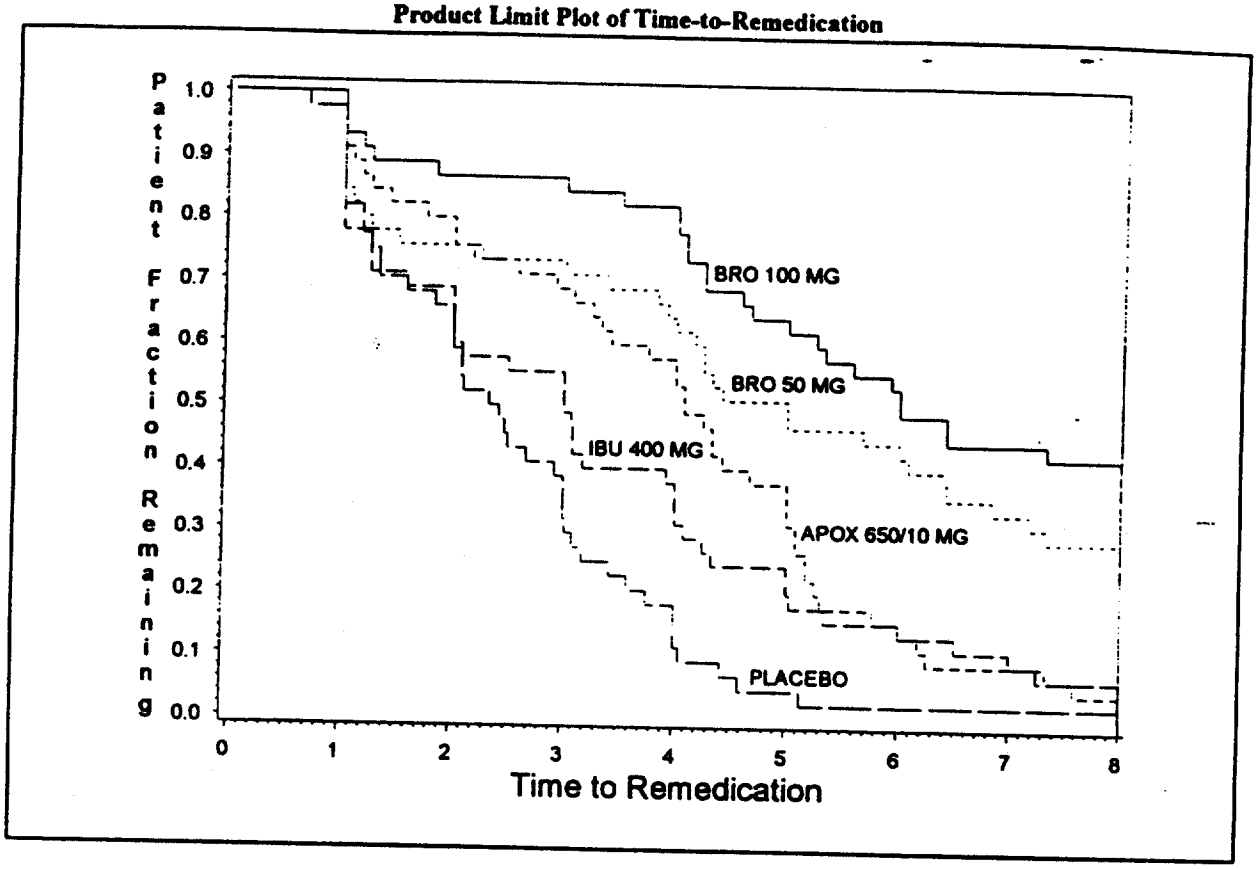


Table 5. Duration of Pain Relief (dur-PR)

Treatment	Calculated Time-to-Remedication	
	Mean h:min[a]	95%-CI h:min[b]
Bromfenac 100 mg	6:16 (A)[c]	5:27 - 7:05
Bromfenac 50 mg	5:13 (A)	4:20 - 6:06
APOX 650/10 mg	4:07 (B)	3:30 - 4:44
Ibuprofen 400 mg	3:32 (BC)	2:51 - 4:13
Placebo	2:46 (C)	2:15 - 3:17

(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 100 mg	4:05 (3:30, 5:20)	6:25 (5:00, >8hr)	>8hr (NE)
Bromfenac 50 mg	2:15 (1:00, 4:10)	5:00 (4:00, 6:50)	>8hr (6:25, >8hr)
APOX 650/10 mg	2:10 (1:15, 3:45)	4:15 (3:25, 5:00)	5:10 (5:00, 6:10)
Ibuprofen 400 mg	1:15 (1:00, 2:05)	3:04 (2:00, 4:00)	5:00 (4:00, 6:30)
Placebo	1:20 (1:00, 2:05)	2:29 (2:00, 3:01)	3:45 (3:00, 4:03)

NE: Not estimable.

LABELING REVIEW OF NDA

Original

NDA #20-535
Review #1

Submission Date: 7/19/96
Review Date: 8/12/96

Generic name: bromfenac sodium capsules

Proposed trade name: DURACT Capsules

Chemical name: benzene acetic acid, 2-amino-3-(4-bromobenzyl)-, monosodium salt, sesquihydrate

Sponsor:

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299
(601) 341-2239

Pharmacologic Category: Nonsteroidal anti-inflammatory drug (NSAID)

Proposed Indication: For the short-term management of pain

Dosage Form(s): 25 mg and 50 mg (as the base) capsules

Route of Administration: Oral

Submitted: Draft blister pack, container and carton labels for the following:

Type of label	package size	as the base 25 mg	as the base 50 mg
Physician Sample Blister Card Carton	Blister card of 2 tablets	X	X
Physician Sample Blister Card	6 blister cards/sheet	X	X
Unit Dose	2 Rows of 5	X	X
Unit Dose Carton	100s	X	X
Carton	100s	X	X
Container	100s	X	X

Reviewer's Comment: In the Medical Officer's review, MO indicated the approval of the 50 mg dosage form should be deferred until it is known how typical meals affect bioavailability, and until the clinical utility of such a dose is demonstrated. Thus labeling for this has not been reviewed.

Reviewer recommended additions are identified by shading. Reviewer recommended deletions are identified by ~~a single strike out line~~.

Unit Carton (Sample)

(MAIN PANEL)
NDA 0008-093-02

1 Blister Card

Reviewer's comment: This statement is not substantiated by reviews.
Duract™ (bromfenac sodium ~~capsules~~) containing 2 Capsules

~~equivalent to~~
25 mg
~~bromfenac~~

Caution: Federal law prohibits dispensing without prescription.

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company

(REMAINDER OF TEXT)
Physician sample: Not for sale
Each capsule contains
~~28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium.~~
Usual dosage: See ~~: package insert.~~
Store at controlled room temperature, 20^0 to 25^0 C (68^0 to 77^0F), protected from moisture and light.
Retain in carton until time of use.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories

LOT EXP

Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

Made and printed in USA

UK21747-1

NDA #20-535

Blister Card - 2s with 6 blister cards per sheet

FRONT

DURACT
(Bromfenca sodium capsules)
equivalent to 25 mg bromfenac

Reviewer's comment: The "25 mg" can be more promenient.

BACK

NDC 0008-0892-02

2 Capsules

Physician sample: Not for sale

Each capsule contain:
28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium.

Usual dosage: See package insert.

Caution: Federal law prohibits dispensing without prescription.

Store at controlled room temperature, 20^0 to 25^0 C (68^0 to 77^0F), protected from moisture and light.

Retain in carton until time of use.

Lot Exp

Wyeth Laboratories Inc.
A Wyeth-ayerst Company
Philadelphia, PA 19101

AN 528-1

Unit Dose Blister

NDC #0008-0892-XX
Duract™
(bromfenac sodium capsules)

25 mg
of the base
Wyeth® Phila.
Lot and Exp.

Unit Dose Carton

(MAIN PANEL)
NDA 0008-0892-99
Duract™ (bromfenac sodium capsules)
equivalent to
25 mg bromfenac

100 Capsules
10 Redipak® Blister
Strips of 10 Capsules

Caution: Federal law prohibits dispensing without prescription.

Wyeth Laboratories Inc.
A Wyeth-ayerst Company

(REMAINDER OF TEXT)

Each capsule contains
28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium.

Usual dosage: See package insert

Store at controlled room temperature, 20° to 25° C (68° to 77°F), protected from moisture and light.

Retain in carton until time of use.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories

Wyeth Laboratories Inc.
A Wyeth-ayerst Company
Philadelphia, PA 19101

Made and printed in USA

UK21732-1

Lot and Exp on side panel with bar code.

NDA #20-535

Carton for bottle of 100s

(MAIN PANEL)

NDA 0008-0892-81
Duract™ (bromfenac sodium capsules)

100 Capsules

equivalent to
25 mg bromfenac

Caution: Federal law prohibits dispensing without prescription.

Wyeth Laboratories Inc.
A Wyeth-ayerst Company

(REMAINDER OF TEXT)

Each capsule contains
28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium.

Usual dosage: See package insert

Store at controlled room temperature, 20° to 25° C (68° to 77°F), protected from moisture and light.

Dispense in a tight, light-resistant container.

Retain in carton until time of use.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories

Wyeth Laboratories Inc.
A Wyeth-ayerst Company
Philadelphia, PA 19101

Made and printed in USA

UK21593-1

Lot and Exp on side panel with bar code.

Container labels for bottle of 100s

(MAIN PANEL)

NDA 0008-0892-81 100 Capsules
Duract™ (bromfenac sodium capsules)
equivalent to
25 mg bromfenac

SEALED FOR YOUR PROTECTION

Caution: Federal law prohibits dispensing without prescription.

Wyeth Laboratories Inc.
A Wyeth-ayerst Company

(LEFT SIDE PANEL)

Each capsule contains
28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium.

Usual dosage: See package insert

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories

Wyeth Laboratories Inc. Made and printed in USA

A Wyeth-ayerst Company
Philadelphia, PA 19101 U0892-81-1

(RIGHT SIDE PANEL)

Store at controlled room temperature, 20° to 25° C (68° to 77°F), protected from moisture and light.

Dispense in tight, light-resistant container.

Retain in carton until time of use.

Lot and Exp on side panel with bar code.

Recommendation: Inform the sponsor of the above revisions and request the sponsor to submit draft labels identical to the above draft labels based on their July 19, 1996 submission.

Marina Y. Chang, R. Ph.

John E Hyde 9-26-96

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

cc: orig NDA
HFD-550
HFD-340
HFD-550/MO/Widmark
HFD-550/MO/Hyde
HFD-550/Div Dir/Chambers
HFD-550/SChem/Patel
HFD-550/SPharm/Chen
HFD-550/Clin/Chang
HFD-550/CSO/Koerner

APPEARS THIS WAY
ON ORIGINAL

Review of DURACT Labeling Revision

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

NDA #: 20-535
SUBMISSION DATE: Feb. 15, 1996. TYPE: Major Amendment-Labeling
REVIEW DATE: July 31, 1996.
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.

NAME: DURACT (Bromfenac sodium) capsules.
SPONSOR: Wyeth-Ayerst
PHARMACOLOGICAL CATEGORY: NSAID
PROPOSED INDICATIONS: Analgesia, dysmenorrhea.
DOSAGE FORM & ROUTE: Capsules, 25 and 50 mg, oral
NDA DRUG CLASSIFICATION: 1-S
RELATED REVIEWS: Original NDA approvable package, Dec., 1995.

RECEIVED: HFD-550: 2/15/96, Reviewer : 2/23/96.
CSO: C. Koerner

MATERIALS REVIEWED: One volume, dated 2/14/96, including: proposed revised labeling, comparisons with the labeling of the 12/28/95 approvable letter, comments on the labeling, re-analysis of dysmenorrhea study AHR-06-US

Background

Bromfenac is a new molecular entity NSAID (non-steroidal anti-inflammatory drug). The NDA was submitted on 12/29/94. The original submission sought indications for analgesia, dysmenorrhea and osteoarthritis. During the review, several substantial modifications were made to the labeling as follows:

Osteoarthritis: At the time of the filing decision, it was called to the sponsor's attention that there was insufficient patient exposure and safety data to support an osteoarthritis indication. The sponsor agreed to withdraw that indication.

Dysmenorrhea: The submission offered three studies in dysmenorrhea (AHR-06, 792A-304 and 792A-307) as substantial evidence for a dysmenorrhea indication. Inspections by DSI led to the disqualification of study AHR-06-US because of lost original records at one of the study sites (Dr. McDonald), and disqualification of study 792A-307 due to an unresolved problem with cracking capsules and missing correspondence. The indication was not approvable because only one study could be accepted.

Hepatic Toxicity: Reviewers were concerned about the frequency and severity of liver enzyme elevations in the arthritis trials and decided it would be prudent to limit therapy to short-term use. Consequently, a hepatic toxicity warning was included in the labeling, references to long-term therapy were removed form the labeling, and a boxed warning was added to assure that clinicians were alerted to the special limitations on use of this NSAID and the risk of chronic use.

Maximum daily dose: Since there was insufficient exposure to daily doses of 200 mg and above, the maximum daily dose was reduced from 200 mg to 150 mg.

An approvable letter was issued 12/28/95. The conditions for approval were: modification of the labeling to make the changes described above, resolution of Chemistry and EA deficiencies, and designation of a tradename. The Chemistry deficiencies were resolved with a submission dated 12/15/95, and the EA response was approved on 2/16/96. The tradename, DURACT, was cleared by the nomenclature committee in January, 1996.

There were a few other noteworthy items about the submission:

1. Bromfenac showed a profound food effect, at least with a high-fat meal: Bioavailability was reduced by more than half, and an effect could be seen when the drug was given between 1/2 hour before or 3 1/2 hours after the meal.

2. Although the terminal elimination half-life is about 1.5 hours, the median duration of action of a 25 mg dose was over 6 hours.

3. One of the analgesia studies (792A-306) was also disqualified following a DSI inspection, but there was a sufficient number of other studies to provide substantial evidence for an analgesic indication.

4. In the dysmenorrhea study 792A-304, a 10 mg dose performed comparably to a 50 mg bromfenac dose and naproxen 550 mg. In dysmenorrhea study AHR-06 (disqualified) even the 5 mg dose of bromfenac appeared to be efficacious at 2 hours and beyond.

The Current Submission

In response to the approvable letter, the sponsor submitted a modification of the 12/28/95 labeling. The sponsor requested 35 specific changes, and provided supporting comments and information. The major issues were:

1. The sponsor seeks to restore the dysmenorrhea indication by providing a re-analysis of Study AHR-06 with data from the disqualified site removed. In the re-analyzed study (Attachment IV, pp. 153-160), bromfenac 25 mg fed and fasted performed similarly and both beat placebo. Bromfenac 5 mg fed and fasted beat placebo fasted, but not placebo fed. The Bromfenac 5 mg fed pain profile was like that of the higher doses; while the 5 mg fasted profile

was numerically lower, but not statistically different from, the other active treatments.

2. The sponsor takes issue with the hepatotoxicity assessment and seeks to remove the boxed warning and the limitation on duration of use, but does include some monitoring recommendations. The sponsor also seeks to re-instate references to chronic use in several places in the labeling. The sponsor compared rates of liver enzyme elevations to the historical rates for ASA, diclofenac, ibuprofen and sulindac using data from NDA 18-922 (etodolac). The data are presented in Tables 11-13 (pp. 97-98) and Figures 1-3 (pp. 99-100) of the submission. They suggest that the rate for bromfenac liver enzyme elevations is greater than for ibuprofen, but less than that for diclofenac, ASA or sulindac.

DISCUSSION:

Issues Raised by Sponsor

Dysmenorrhea
DSI was asked to inspect one of the remaining sites (Dr. Macy) of Study AHR-06. The site was disqualified due to missing and inaccurate records. Thus Study AHR-06 remains unusable. The dysmenorrhea indication still has substantial evidence from only one study (792A-304).

Hepatic Toxicity
The sponsor's historical comparisons are interesting but difficult to interpret. Overall incidence of hepatic events in a study can be affected by the disease being treated (hepatic effects of ASA are seen more in RA than in OA trials, diclofenac hepatotoxicity is seen more in OA than in RA trials), the frequency of monitoring, the propensity to remove patients from the study for liver enzyme changes, and unknown patient population factors. The relative rates of liver enzyme elevations presented in the sponsor's tables seem not in accord with the findings of the head-to-head studies of the NDA (in which ASA was used in OA, diclofenac in RA).

The agency remains concerned about the few sentinel cases of severe liver enzyme elevations and the cases with relatively early enzyme elevations. (An addition case of florid enzyme elevation was included as a 10-day report in the safety update.) While these may have been unlucky events that might be diluted with greater exposure experience, it is hard to tell with the data currently available. Just as there is room for downside correction with greater exposure experience, there is ample opening for upside correction as well. The data base of chronic use is relatively small for a new NSAID. Fewer than one thousand chronically exposed patients were in the initial NDA submission, slightly over that number were in the update. All other approved NSAIDs, apart from ketoprofen, have an arthritis indication and at least the more recent applications were supported with relatively large safety databases. NSAIDs are widely used, and they are a mainstay in the treatment of OA and RA. Since bromfenac at this point has only an

analgesic indication, it seems imprudent to open the doors to extensive use when there have been early warning signs, and the safety experience is yet too small to provide much reassurance.

Other Sponsor Issues
Comments on minor issues in the labeling are included in the attached REVIEWER'S ANNOTATIONS FOR THE LABELING.

Additional Issues

In the process of revisiting the labeling, some additional issues were raised by the reviewing division. Some minor editorial and organizational changes were made to conform with the division's current labeling practices. In addition two more substantial changes were made:

The 50 mg dosage form
In no case did a 50 mg dose provide better acute analgesia than the 25 mg dose (although in AHR-22, 50 mg appeared to have a somewhat longer duration). In the fed-fasted study (792A-311-III), increasing from 25 to 50 mg produced a numerical but not statistically significant improvement in pain scores. From the evidence available in the NDA, the argument that can be made for using a 50 mg dose is that, with a high-fat meal, a 50 mg dose will provide a kinetic profile similar to that of a 25 mg dose in a fasted patient. It is possible that a more "typical" lower fat meal would produce less of a feeding effect. Data from the (disqualified) dysmenorrhea fed/fasted crossover study suggested that food consumption does not have a big a clinical effect. Even the sponsor argues that the feeding effect may not be that important clinically (Appendix II, pp. 124-144). However, patients should be alerted at least to pay attention to how bromfenac is taken in relation to food, at least until the issue is clarified.

Without good information on the clinical impact of normal meals, the need for a 50 mg dosage form is questionable, and its availability invites the risk of encouraging excessive dosing. In fact, if the dysmenorrhea indication is pursued, and if the results are consistent with those of the studies already performed, then the availability of a smaller (e.g., 10 mg), rather than larger, dosage form would be in order.

Special Studies section of the labeling
Following a reassessment of divisional labeling practice, it was decided that the inclusion of the type of material in the Special Studies section (clinical studies that are unreplicated and of unknown clinical significance) was not supported by labeling regulations, and should be removed.

CONCLUSIONS:
The dysmenorrhea indication has not been established, because Study AHR-06 remains disqualified.

The potential for hepatotoxicity remains a concern.

The support for using a 50 mg dosage form is weak, so that the need for a 50 mg dosage form is questionable.

The labeling needs some other editing and reorganization to remove redundancy and make it in accord with current division labeling practice (see also attached REVIEWER'S ANNOTATIONS FOR THE LABELING).

RECOMMENDATIONS:
The labeling should not include an indication for dysmenorrhea.

The hepatic warnings and limitations on duration of use should remain in the labeling.

The approval of a 50 mg dosage form should be deferred at least until it is known how typical meals affect bioavailability, and preferably until the clinical utility of such a dose is demonstrated.

The sponsor should be issued an approvable letter with the condition for approval being acceptance of the Agency's 8/96 revision of the labeling of 12/28/95.

John E Hyde

John E. Hyde, PhD, MD

CC:
Orig NDA # 20-535
HFD-550/Div File
HFD-340
HFD-550/CSO/CKoerner
HFD-550/Chem/BHo
HFD-550/Pharm/CChen
HFD-550/Pharm/JYang
HFD-550/Stat/RStein
HFD-550/Biopharm/DBashaw
HFD-550/MO/JHyde
HFD-550/MO/RWidmark

WHE 8/20/96

REVIEWER'S ANNOTATIONS FOR THE LABELING
DURACT, NDA 20-535

(GENERAL COMMENTS: In several places the labeling has been shortened by eliminating information duplicated in other parts of the labeling, and by paring down text to emphasize "pertinent positive" findings over "lack-of-relationship" findings.)

[BOXED WARNING]
The Agency remains concerned about the potential for hepatic injury with bromfenac. NSAIDs are widely used for chronic conditions, and all approved NSAIDs except ketorolac have a chronic use (arthritis) indication. It is important that physicians are alerted to the duration-of-use restriction and to the potential risk with chronic use.

[DESCRIPTION]
The description of the 50 mg capsule has been removed -- see remarks in the labeling revision review.

[SPECIAL STUDIES]
The SPECIAL STUDIES section has been removed because the division has determined that inclusion of such information is not supported by labeling regulations.

[CLINICAL STUDIES]
Descriptions of the dysmenorrhea studies and chronic use studies remain excluded because substantial evidence has not been provided for the dysmenorrhea indication, and chronic use is not recommended.

Comparisons to ketorolac IM are not included. The study involving ketorolac (792A-302) had a strong placebo response, did not show any separation between treatments until 2 hours, and all active controls performed very similarly. The study appears to lack upside sensitivity and does not provide a reliable basis for making comparisons.

[INDICATIONS AND USAGE]
This section re-instates the wording of the 12/95 approvable letter, since the dysmenorrhea indication is still not established and the concern about chronic use remains.

[WARNINGS-Hepatic Toxicity]
This section remains as in the 12/95 approvable letter. The agency feels the safer way to deal with the potential hepatotoxicity is to limit duration of use rather than recommending a vaguely-defined monitoring program.

[WARNINGS-Risk of Gastrointestinal Ulceration...]
The class labeling should be adapted to reflect the duration of use limitations, i.e., the portions that refer to chronic use have been omitted.

[PRECAUTIONS-Hepatic Effects]
The section has been removed since it duplicates information found elsewhere in the labeling (in CLINICAL PHARMACOLOGY-Pharmacokinetics and WARNINGS-Hepatic Toxicity).

[PRECAUTIONS-Information for Patients]
Information about the food effect is re-instated. Until information is available on the effect on bromfenac bioavailability of a "realistic" meal, patients should be alerted to pay attention to how the drug is taken in relation to meals because it may have an impact on effectiveness.

[PRECAUTIONS-Laboratory Tests]
The discussion of signs and symptoms of GI ulceration and bleeding has been omitted, although it has appeared in this section in other NSAID labeling in the past. That information duplicates information elsewhere in the labeling, and it does not specifically address laboratory testing.

Since chronic use is not recommended, the portion describing that use has be excluded.

[PRECAUTIONS-Drug Interactions]
This section has been simplified to present only those cases in which bromfenac and other drugs interact. Information on antacid effect is already included in the CLINICAL PHARMACOLOGY-Pharmacokinetics section.

[ADVERSE EVENTS]
Liver enzyme elevation of more than borderline should be retained in the 3-9% category. Significant abnormalities of >3xULN are in the less than 1% category. Since limited duration of use in recommend, special discussion of the rates for chronic use are not needed, and may even be misconstrued as being intended to guide chronic use.

[DOSAGE AND ADMINISTRATION]
Discussion of dysmenorrhea is not included because the indication has not been established.

[HOW SUPPLIED]
Reference to the 50 mg capsule has been omitted -- see discussion in the labeling revision review.

23 pages of

draft Labeling

Redacted

Addition Pkg

MEMORANDUM

November 14, 1996

To: Dr. M. Lumpkin
Through: Dr. W. Chambers
From: R.M. Widmark
Copies: Dr. M. Weintraub
Dr. J. Hyde
Chin Koerner

re: Hepatotoxicity of bromfenac compared to diclofenac in the original NDA submissions

The subject of hepatotoxicity of bromfenac in comparison to that of diclofenac in the original submissions arose because of a difference of opinion between the reviewing division and Wyeth-Ayerst regarding the labeling of bromfenac as an analgesic for short-term use.

The Bromfenac Submission

The submission contained 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 (osteoarthritis), 305 (rheumatoid arthritis) and 309 (osteoarthritis), comprising over 800 patients. The duration of these trials was 52 weeks.

In summary, out of a total of 830 patients, there were 19 who had ALT elevations exceeding 3 times the ULN (Upper Limit of Normal) and 4 patients with ALT elevations exceeding 8 times the ULN, which results in 2.8% (23/830) of medically significant ALT elevations.

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. 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.
The time when the ALT elevations occurred was established only for 13 patients, as shown in the attached Graph 1. The squares represent the greater-than-3-times-the-ULN elevations of ALT: as can be seen, substantial abnormalities occurred in 5 patients around Day 30 of treatment. From Graph 2 it becomes evident that the great majority of ALT elevations (of >3 times the ULN) occurred in the first 90 days of treatment.

The Diclofenac Submission

For the liver safety of diclofenac, the submission contained laboratory data on SGOT (AST) and alkaline phosphatase, not on SGPT (ALT), which forced us to assess liver safety through the non-liver specific AST test. The rheumatoid arthritis and osteoarthritis trials were grouped in short-term (up to 3 months) and long-term (up to 5 years) studies, with the following rate of AST elevations exceeding 3 times the ULN.

AST elevations ≥3 times the ULN for diclofenac-treated patients in the original NDA submission:

Osteoarthritis	Short-term	15/448	3.3%
Osteoarthritis	Long-term	25/561	4.5%
Rheumatoid arthritis	Short-term	4/461	0.9%
Rheumatoid arthritis	Long-term	10/465	2.2%
Total	Overall	54/1935	2.8%

At the time of the review (August 1987), despite the lack of a liver-specific laboratory test, we concluded that diclofenac showed signs of hepatotoxicity, with osteoarthritis patients at higher risk than rheumatoid arthritis patients, and with evidence that the risk increases with the duration of treatment with diclofenac. The Sponsor (CIBA-Geigy) disagreed with us, but confirmed our findings in a postmarketing study. In addition, there was an extensive marketing experience of diclofenac in Europe available to us (for 10 years the best-selling NSAID on the European market) and, despite all of that, only our review discovered that diclofenac has a liver problem, which was recently confirmed by a paper characterizing the hepatotoxicity of diclofenac as being a metabolic idiosyncrasy.

Comments

In their argumentation, Wyeth-Ayerst presents their own diclofenac data which did not all come from the NDA submission for bromfenac but were taken from another NDA submission (ketoprofen extended-release) in osteoarthritis patients, who - we now know for sure - represent patients at high risk. The diclofenac example actually is a perfect example that in our safety review of NDA study we usually do not get definitive answers based on unequivocal data but are forced to interpret "flagging" events. We think that in the case of bromfenac, we have seen a "liver flag" that can be only fully explored through responsible marketing of the drug.

As an example of the usual hepatic pattern of an NSAID, we have looked at the liver safety review of Wyeth-Ayerst's etodolac (LODINE). ALT elevations ≥3 times the ULN were seen in 9 out of 1150 rheumatoid arthritis patients (= 0.8%) and in 4 out of 1331 osteoarthritis patients (= 0.3%): Subsequent postmarketing data have not shown any unusual hepatotoxicity of LODINE.

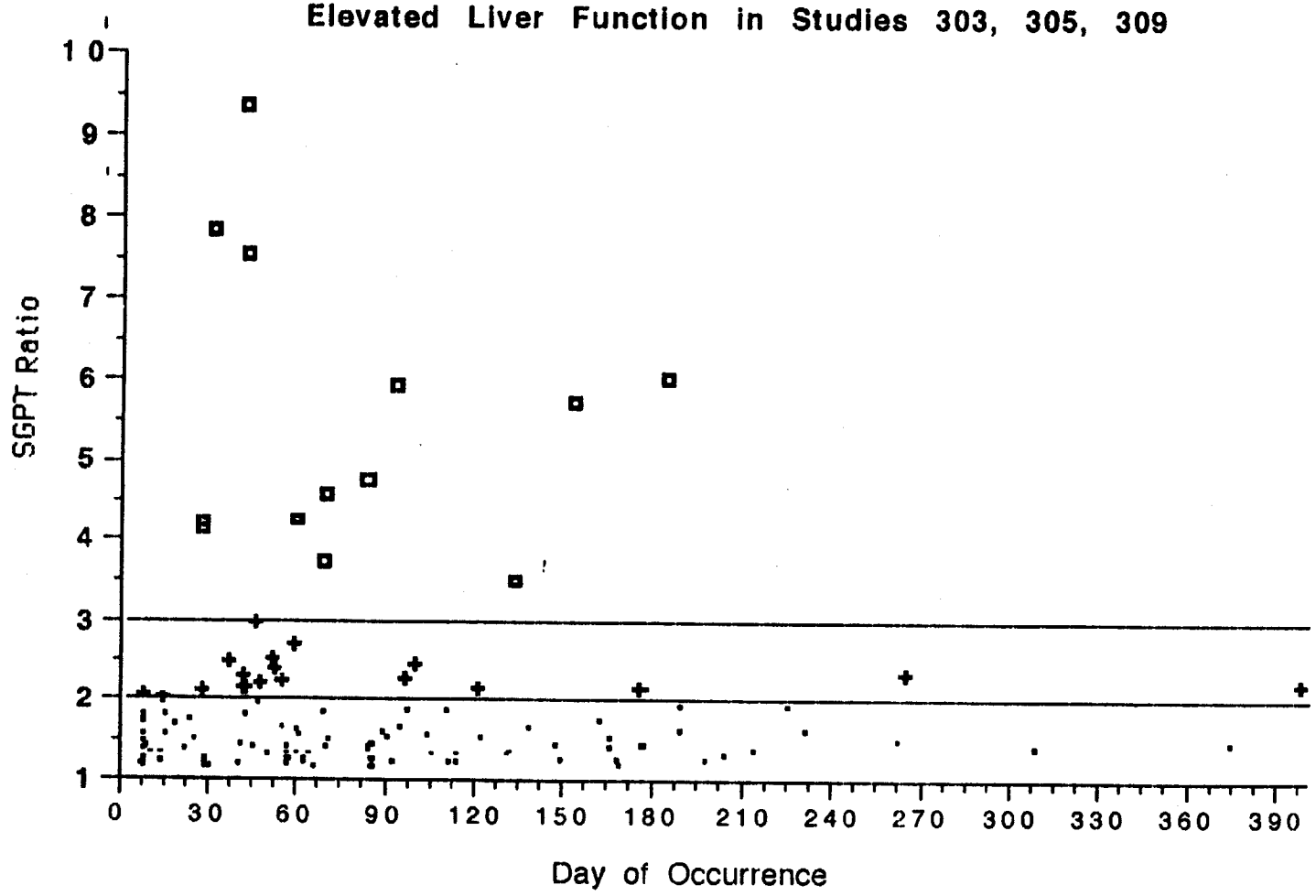
The company proposes a label that states that bromfenac is for short-term management of pain; when given longer than 30 days, the patient should be monitored for liver abnormalities. The company would like a label that actually puts the onus on the prescribing physician because, if severe and maybe fatal liver toxicity of bromfenac will occur in treatments longer that 30 days, the physician will be sued and will be found liable if he/she did not 'monitor' for liver damage. Wyeth-Ayerst will be in the clear, because "it is in the label."

I hope that this short memo will help you to make the right decision in this dispute. Please, do not hesitate to call on me, if you think I could be of any assistance.

Rudolph M. Widmark, MO

APPEARS THIS WAY
ON ORIGINAL

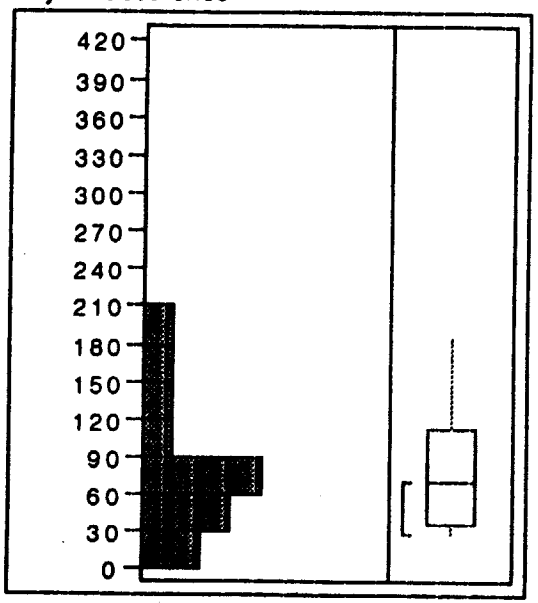
Graph 1


Elevated Liver Function in Studies 303, 305, 309
SGPT Ratio
10
9
8
7
6
5
4
3
2
1
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Day of Occurrence

GRAPH 2

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

Bromfenac Safety Update

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

NDA #: 20-535
SUBMISSION DATE: December 11, 1995. TYPE: NDA Safety Update
REVIEW DATE: August 1, 1996.
REVIEWER: John Hyde, Ph.D., M.D., Medical Officer.

NAME: DURACT (bromfenac sodium) capsules.
SPONSOR: Wyeth-Ayerst
PHARMACOLOGIC CATEGORY: NSAID
PROPOSED INDICATIONS: Analgesia, Dysmenorrhea
DOSAGE FORM & ROUTE: Capsules, 25 mg & 50 mg, oral
NDA DRUG CLASSIFICATION: 1-S
RELATED REVIEWS: Original NDA package of 12/95.
RECEIVED: HFD-550: 12/15/95
CSO: C. Koerner

MATERIALS REVIEWED: 1) Submission dated 12/11/95 consisting of 13 volumes including a one-volume summary and 12 volumes of case report forms. 2.) Submission dated 4/19/96 consisting of a volume containing an analysis of patients with positive fecal occult blood.

TOTAL EXPOSURE TO BROMFENAC

The bulk of the additional chronic safety data comes from a new low-dose OA study (792A-314) having double-blind and open-label segments. Some additional exposure comes from the open-label extension of OA study 792A-309. There are also data from 116 patients in a single dose cancer pain trial. Two additional single-dose studies were recently completed but the blind was not yet broken, so breakdown by treatment was not available for those studies.

The change in total chronic exposure is shown below:

Original NDA	Update	% Increase
926 pts	1354 pts	46%
5948 pt-months	9332 pt-months	57%

The sources of the patients in the chronic exposure data base are set out in the following table. For simplicity, different regimens have the same daily dose have been lumped, and details of control group sample sizes have been omitted:

Source of Patients for Chronic Bromfenac Exposure Data

Study No.	Disease	N	Bromfenac Daily Dose	Design	Controls
18	OA	26 26 22	100 mg/d 40 mg/d 20 mg/d	6 week DB	ASA 4000 mg/d ASA 2600 mg/d Placebo
303	OA	156 78	100 mg/d 50 mg/d	6 week DB 1 yr OL (334 on Brom)	Nap 1000 mg/d Placebo
309	OA	108	150 mg/d	4 week DB 1 year DB vs. Ibu (152 on Brom 75-225 mg/d) 4 yr OL	Ibu 1800 mg/d Placebo
314	OA	78 78 79	50 mg/d 20 mg/d 10 mg/d	4 week DB 2 year OL (339 on Brom)	Nap 1000 mg/d Placebo
23	RA	6 6 6	200 mg/d 100 mg/d 40 mg/d	8 week DB	none
305	RA	154 152	200 mg/d 100 mg/d	36 week DB	Diclofenac 150 mg/d

DB=double-blind, OL=open-label, Brom=bromfenac, Nap=naproxen, Ibu=ibuprofen

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

Cumulative Exposure in Chronic Studies

	≥ 31 days	≥ 61 days	≥ 91 days	≥181 days	> 360 days
Original NDA	799	638	578	474	193
Safety Update	1195	1015	927	734	247

A more detailed breakdown of the chronic study exposure is provided in sponsor's table 3.2 on p. 23 of teh submission. Of note from that table is that for doses of 200 mg/day and above, 231 patients were exposed initially and 198 were exposed for a month or more.

DEATHS

In the original submission, two cardiovascular deaths were reported. Both were in OA studies. In the update, two additional deaths were reported in patients in OA study 314. Descriptions of the fatal cases are as follows:

> Patient 31411-001, a 76 year old man had a history that included hypertension, renal insufficiency secondary to diuretics, peripheral edema, phlebitis, depression, and cellulitis of the legs. Concomitant medication included phenoxymethylpenicillin potassium, fluoxetine and indapamide. The patient received placebo in Segment I, and he was in Segment II for 441 days (predominant dose-bromfenac 75 mg/day) before expiring due to an acute myocardial infarction. No other adverse events were reported in Segment II.

Patient 31420-002, a 66-year-old women, had a history that included tobacco abuse and recovered alcohol abuse, cerebral vascular accident, bilateral endarterectomies, C.O.P.D., surgery of both hips, osteoporosis, C.A.D., and multiple other medical problems. Concomitant medication included beclomethasone, cefotaxime, dexamethasone, meperidine, oxycodone hydrochloride, and prochlorperazine edisylate. She received naproxen 500 mg b.i.d. for 28 days in Segment I and was receiving bromfenac for 472 days in Segment II (predominant dose-200 mg/day) when she expired due to carcinoma of the larynx. The patient had had intermittent hoarseness for nine month before her death and was hospitalized for a compression fracture of T-5 due to osteoporosis 18 days before her death. C-T Scan of the chest showed C.O.P.D. with tracheal obstruction, a subglottic tumor, and bilateral lobe infiltrates with atelectasis secondary to obstruction. A biopsy of the right vocal cord showed invasive moderately well differentiated grade II squamous cell carcinoma. The patient's hematocrit fell and she was transfused. According to the hospital records the trachea was almost completely occluded by the tumor. No explanation for the falling hematocrit was found.

It is unlikely that the underlying cause of death in either of these cases was related to bromfenac. However it is a possibility that NSAID enteropathy might have contributed to the unexplained blood loss in the second case and could have played a role in the immediate cause of death.

10-DAY REPORTS

The update included two 10-day safety reports. One was a case of postoperative bleeding; the second was a case of hepatitis with hyperbilirubinemia:

Patient 31421-004 was a 72 y.o. male taking bromfenac 150 mg/day for 1 year for OA. Bromfenac was stopped two days before entering the hospital for total knee arthroplasty. He had considerable postoperative bleeding requiring transfusion of 5 units of blood or red cells. Bromfenac was restarted 3 days after surgery.

Patient 31426-016 was a 71 y.o. female taking bromfenac 150 mg/day for 15 mo. for OA. She had a history of gallstones. She was reported to have asymptomatic anicteric elevation of bilirubin to 5.6 associated with elevation of ALT to 575 (16xULN), AST of 532 (15xULN), Alk. Phos. of 2.2xULN , and 7.9% eosinophilia (nl. <6%). Additional studies were pending. The patient had a transient elevation of ALT two months previously during a hospitalization for hiatal hernia repair.

NEOPLASMS

No new listings of neoplasms was provided. However the COSTART listings included a total of 26 cases in neoplasm/carcinoma categories for bromfenac. This is a 37% increase over the number reported in the NDA; less than the increase in this update in either numbers exposed or patient-days.

PERFORATIONS, ULCERS AND BLEEDS (PUBs)

For the original safety summary, the sponsor reviewed cases with study event COSTART terms suggesting PUBs. Nineteen cases of ulcers or bleeds were identified. There were no perforations. A lifetable analysis suggested the rates for PUB for bromfenac was in the range represented by ibuprofen and diclofenac.

There were 12 new PUB events (63% increase from NDA) of which 7 led to discontinuation. There were no perforations. The cases are summarized in table 5.4 on pp. 61-64 of the submission. Of the 5 events occurring within 2 months of therapy, two were "melena" with negative hemocculs, one was a duodenal ulcer in an H. pylori positive patient, one was an esophageal ulcer in a patient with pre-study dysphagia, and one was a 74 y.o. female with gastric ulcer and hemoccult positive stools on day 15 of bromfenac. No lifetable analysis was provided in this update.

In the original safety summary it was noted that the COSTART terms used in the search for PUBs did not include STOOLS ABNORMAL. That term was found to identify several patients with hemoccult positive stools who where not captured with the other COSTART terms. The sponsor was asked to review this class of patients as well. The results were reported in the 4/19/96 submission. In the 100 bromfenac patients with hemoccult positive stools, 4 showed significant (≥2) changes in hemoglobin. Rates for hemoccult positivity and hemoglobin change did not demonstrate any clear differences from the active comparators (from Table 1 of the 4/19/96 submission):

Treatment	N	% Hemoccult positive	% with Hgb change ≥2
Bromfenac (All doses)	833	12.0	0.5
200-225 mg/d	191	14.1	1.0
150-199 mg/d	119	11.8	0.0
76-149 mg/d	510	10.6	0.4
<= 75 mg/d	88	5.7	0.0
Ibuprofen	159	17.6	0.6
Diclofenac	78	11.5	1.3
Naproxen	83	13.3	0.0
Placebo	189	4.8	0.5

CLINICAL LABORATORY FINDINGS

In the NDA there were 24 patients with significant (≥ 3xULN) elevation of AST or ALT, and four with severe elevations ≥ 8xULN. In the update there are 34 (up 42%) with significant elevations, and 6 (up 50%) with severe elevations. One of the two additional cases of severe elevations is

noteworthy in that it provided an example of a dechallenge/rechallenge experiment:

> Patient 31425-0014 was a64 y.o. female S/P cholecystectomy taking bromfenac for OA. She took bromfenac through the blind and open phase for a total of 2 months when ALT became elevated over 8xULN. Bilirubin and alk. phos. were normal. Drug was stopped temporarily and liver enzyme changes resolved over 2 weeks. Bromfenac was resumed, and after two month liver enzymes became significantly elevated and she was discontinued from the study.

CONCLUSIONS:
The additional safety experience is consistent with what was seen in the original NDA. The exposure data base with doses 200 mg/day and above is still to small to support consideration of daily dosing greater than 150 mg/day.

RECOMMENDATIONS:
There are no new recommendations to add to those of the original NDA safety review.

John E Hyde

John E. Hyde, PhD, MD

CC:
Orig NDA # 20-535
HFD-550/Div File
HFD-340
HFD-550/CSO/CKoerner
HFD-550/Chem/BHo
HFD-550/Pharm/CChen
HFD-550/Pharm/JYang
HFD-550/Stat/RStein
HFD-550/Biopharm/DBashaw
HFD-550/MO/JHyde
HFD-550/MO/RWidmark

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8/7/96

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MEDICAL OFFICER REVIEW

ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS DIVISION -- HFD-550

NDA #:	20-535
SUBMISSION DATES:	March 3, 1997, and October 18, 1996.
TYPE:	Safety Updates
REVIEW DATE:	July 14, 1997.
REVIEWER:	John Hyde, Ph.D., M.D.
NAME:	DURACT (bromfenac sodium)
SPONSOR:	Wyeth-Ayerst Research
PHARMACOLOGIC CATEGORY:	NSAID
PROPOSED INDICATIONS:	Analgesia
DOSAGE FORM & ROUTE:	Capsules, 25 mg, oral
NDA DRUG CLASSIFICATION:	1S
RELATED REVIEWS:	Original NDA Package of 12/95 Safety Update Review of 8/1/96
CSO:	C. Koerner
MATERIALS REVIEWED:	March 3, '97, Safety Update October 18, '97, Safety Update

RESUME:

As of the 3/3/97 safety update, 1358 patients have been exposed, for a total of 14,098 patient-months of exposure. This represents only 4 more patients than covered in the last written review, but it is an increase of 51% in patient-months.

There have been four additional deaths, two from cancer, one from septic shock, and one from complications of arteriography. None appears related to bromfenac.

There have been four more PUB discontinuations. Except for a gastric ulcer after 112 days, the others (DU, melena and erosive gastritis) came after a year of treatment.

There were five more reports of SGPT > 3xULN, with one of them having SGPT > 8xULN and increased bilirubin after 455 days of treatment. This last case was noted as a 10-day report in the previous safety update review; the enzyme elevations resolved.

CONCLUSIONS:
The additional safety experience is consistent with what was seen in the original NDA and earlier updates.

RECOMMENDATIONS:
There are no new recommendations to add to those of the original NDA safety review.

Orig NDA # 20-535
HFD-550/Div File
HFD-340
HFD-550/CSO/Koerner
HFD-550/MO/JHyde

John E Hyde 7-14-97
John E. Hyde, Ph.D., M.D.

7/14/97

Executive Summary: Statistics

Drug Name: **Bromfenac**, 25 & 50 mg capsules
NDA #: 20,535
Sponsor: Wyeth-Ayerst Laboratories
Indication: Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea.
Statistical Review Date: December 18, 1995 (21 page review)

Submission date: Dec. 29, 1995

Reviewing Statistician: Richard A. Stein, PhD
Primary Medical Reviewer: John Hyde, MD; Rudolph Widmark, MD
Consumer Safety Officer: Chin Koerner, CSO

Studies Reviewed

Acute Dental Pain	Acute Post-Operative Pain
AHR-02-US	AHR-05-UK
AHR-16-US	AHR-20-UK
AHR-22-US	792A-302-NZ
792A-301-US	792A-306-US
792A-311-US	

Summary

1. In Dental Pain, substantial statistical evidence of effectiveness was shown for bromfenac 25 and 50 mg in studies AHR-02, AHR-22, and 792A-301.

2. In Postoperative Pain, substantial statistical evidence of effectiveness was shown for bromfenac 25 mg in studies AHR-05 and 792A-302.

   Bromfenac 50 mg was shown statistically effective in study 792A-302. However, the statistical evidence of efficacy found in post-operative surgery study 792A-306 for 50 mg bromfenac is considered invalidated. This recommendation is based on a memorandum dated 12/12/95 from Matthew Thomas, MD, Division of Scientific Investigations, who recommended that this study site not be used to support any efficacy and safety claims for Bromfenac Sodium Capsules.

3. Based on patient data provided by Wyeth on 9/19/95, we can expect some elevated SGPTs of at least 1.2 times the upper limit of normal patient at about 10 days after initiating bromfenac. Some patients went as high as 7 times the upper limit of normal. For patients with elevated SGPT after initiating bromfenac, the median time to highest elevation is about 2 months.

4. "Comparable analgesic effectiveness" for acute pain is currently a medical impression that is not a judgment based on developed statistical criteria.

Richard A. Stein

Richard A. Stein, Ph.D.
Mathematical Statistician

Statistical Review and Evaluation

Dec 19, 1995

NDA #:	20,535
Drug Name:	Bromfenac, 25 & 50 mg capsules
Indication	Management of acute and chronic pain, including pain of osteoarthritis and primary dysmenorrhea.
Sponsor:	Wyeth-Ayerst Laboratories
Sponsor's Letter Dated:	12/29/94
Documents Reviewed:	Vols. 1.1, 1.267, 1.268, 1.284, 1.285, 1.291, 1.294, 1.295, 1.298, 1.305, 1.316, 1.318, 1.321, 1.333, 1.337, 1.348.
Date Received:	1/10/95
Reviewing Statistician:	Richard A. Stein, PhD
Statistical Review Date:	December 18, 1995 (21 page review)
Primary Medical Reviewer:	John Hyde, MD; Rudolph Widmark, MD
Consumer Safety Officer:	Chin Koerner, CSO

I. Introduction

There are 2 sources of statistical information to be found in this submission. In the paper-copy submission, the applicant has followed statistical methodology quite similar to that found in some of the analgesic literature. The NDA statistical methodology has not been defined in many protocols, and so the sponsors adopted statistical methodology is not unreasonable. In the CANDA (Computer Assisted New Drug Application) the applicant has essentially provided analyses requested by HFD-550 reviewers to speed their review.

II. Efficacy Review by Study: Pain and Postoperative Pain studies are examined here.

A. Dental Pain: In summary of the following studies, I conclude that the applicant has shown the effectiveness of bromfenac 25mg and 50mg in studies 792A-302 and 792A-306. Additionally bromfenac 25mg was shown effective in study AHR-16.

1. Study AHR-02-US (pain)

This protocol was a standard randomized, parallel group, double-blind, 3-investigator pain study. Pain evaluations were made at 0, 1/4, 1/2, 1, 1.5, 2, 3, 4, 5, and 6 hours. The 5 treatment groups were (1) bromfenac 50mg, (2) bromfenac 25mg, (3) bromfenac 5mg, (4) Aspirin 650mg, and (5) placebo. It was planned that each investigator (Zola, Kessler, Suchow) recruit 100 patients. The data of Dr. Kessler is inadequate in that only 2/100 patients were recruited. A total of 202 patients was analyzed for efficacy.

The applicant concluded, among other things, Vol. 1.294, page 15, that bromfenac 25mg and 50mg are statistically more effective than placebo.

My own analyses of the patient data provided by the applicant lead me to conclude that 2 5mg and 5 0mg have been shown to be statistically effective analgesic doses of bromfenac in study AHR-02-US. Even the 5mg dose has been shown to be effective statistically.

2. Study AHR-16-US (pain)

By protocol, this was a standard randomized, parallel group, double-blind, 2-investigator pain study conducted under James Forbes. Pain evaluations were made at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The 6 treatment groups were (1) bromfenac 25mg, (2) bromfenac 10mg, (3) bromfenac 5mg, (4) Aspirin 650mg, (5) Ibuprofen

400mg, and (6) placebo. It was planned that sub-investigators (Smith, Schwartz) would recruit a total of 288 patients. A total of 267 patients was analyzed for efficacy. After approximately 120 patients were recruited, the study blind was broken and an "interim analysis was performed. The interim analysis was not adjusted for or reported at the time of the final analysis.

The applicant concluded, among other things, Vol. 1.295, page 25, that bromfenac 5, 10, and 25mg are statistically more effective than placebo.

I believe Study AHR-16_US supports the effectiveness of bromfenac 2 5mg and 50mg.

3. Study AHR-22-US pain)

By protocol, this was a randomized, parallel group, double-blind, 4 sub-investigator, 2 nurse-observer pain study conducted under James Forbes. Pain evaluations were made at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The 7 treatment groups were (1) bromfenac 100mg, (2) bromfenac 50mg, (3) bromfenac 25mg, (4) bromfenac 10mg, (5) Aspirin 650mg, (6) Ibuprofen 400mg, and (7) placebo. It was planned that the investigators (Smith, Gongloff, Schwartz, Smith) would recruit a total of 350 patients. A total of 316 patients was analyzed for efficacy.

Wyeth has concluded that all doses of bromfenac were significantly superior to aspirin 650mg and placebo for the primary efficacy variables. In a 1992 Journal of Clinical Pharmacology and Therapeutics journal article by Forbes et al., it was stated that "All active medications had shown a significant analgesic effect by hour 1 ... Significant analgesia was maintained for 6 hours by 10 mg bromfenac and for 8 hours by the other doses (25, 50, and 10 mg)." My own analyses of the patient data provided by the applicant lead me to essentially the same statistical results.

I conclude that 2 5mg and 5 0mg have been shown to be statistically effective analgesic doses of bromfenac in study AHR-22-US.

4. Study 792A-301-US (pain)

By protocol, this is a randomized, parallel group, double-blind, 2 investigator, study conducted under James Forbes. Pain evaluations were made at 0, 1/2, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The 4 treatment groups were (1) bromfenac 50mg, (2) bromfenac 25mg, (3) naproxen sodium 550mg, and (4) placebo. It was planned that the investigators would recruit a total of 200 patients. Repeat doses would be administered every 8 hours for up to 7 days. A total of 215 patients was analyzed for efficacy.

This study shows the effectiveness of bromfenac 25mg, bromfenac 50mg and naproxen sodium 550mg from 1/2 hour to 8 hour evaluation time inclusive. In fact, from hours 1 to 3 inclusive, bromfenac 25mg was shown to provide statistically more relief from pain than naproxen sodium 550mg.

I conclude that 2 5mg and 5 0mg have been shown to be statistically effective analgesic doses of bromfenac in study 792A-301-US.

5. Study 792A-311-US pain)

Based on the protocol, this is a randomized, parallel group, 3 investigator, pharmacokinetic study conducted in 3 sections essentially in fed and fasted patients under Dr. Stephen Cooper. Pain evaluations were made at 0, 1/4, 1/2, 1, 1 1/2, 2, 3, 4, 5, 6, 7, and 8 hours.

Section I included 6 treatment groups (1) bromfenac 200mg, (2) bromfenac 100mg, (3) bromfenac 50 mg, (4) bromfenac 25mg, (5) bromfenac 5mg, and (6) placebo compared in double-blind fashion. A total of 122 patients was analyzed for efficacy.

Section I I was an open label comparison of 3 different diets with no efficacy data collected.

Section III included 4 treatment groups: (1) bromfenac 50mg fed, (2) bromfenac 25mg fed, (3) bromfenac 25mg fasted, and (4) placebo fed. These 79 patients were studied for 2 hours by one investigator, Dr. Cooper. A total of 80 patients was analyzed for efficacy.

These data provide statistical evidence that support the effectiveness of bromfenac 25mg and 50mg.

B. Postoperative Pain: In summary of the following post-operative pain studies, I conclude that the applicant has shown the statistical effectiveness of bromfenac 25mg in studies AHR-05 and 792A-302. Bromfenac 50mg was shown statistically effective in study 792A-302 and in DSI disqualified study 792A-306.

1. **Study AHR-05-UK** (Postoperative Orthopedic pain)
By protocol, this is a standard randomized, placebo controlled, parallel group, double-blind, single-investigator pain study. Pain evaluations were made at 0, 1/4, 1/2, 1, 1.5, 2, 3, 4, 5, and 6 hours. The 5 treatment groups were (1) bromfenac 25mg, (2) bromfenac 10mg, (3) bromfenac 5mg, (4) Acetaminophen 1000mg, and (5) placebo. It was planned that the investigator (McQuay) recruit 150 patients. A total of 157 patients was analyzed for efficacy.

The applicant concluded, among other things, Vol. 1.284, page 33, that bromfenac 25mg is statistically more effective than placebo. Lacking a bromfenac 50mg treatment group, direct evidence of effectiveness is not available for this study. The applicant also concluded bromfenac 10mg to be shown effective, but not bromfenac 5mg. This study is at least supportive of the effectiveness of bromfenac 25mg and 50mg.

2. **Study AHR-20-UK** (Postoperative Orthopedic pain)
By protocol, this is a standard randomized, non-placebo controlled, parallel group, double-blind, single-investigator pain study. Pain evaluations were made at 0, 1/2, 1, 2, 3, 4, 5, and 6 hours. The 5 treatment groups were (1) bromfenac 25mg, (2) bromfenac 50mg, (3) bromfenac 100mg, (4) ibuprofen 200mg, and (5) ibuprofen 400mg. This study (Bostrom) had 40 patients per treatment group analyzed for efficacy.

Lacking a placebo control group and detecting no statistically significant linear contrast across the 25, 50, and 100 mg treatment groups, this study does not provide substantial evidence of the efficacy of bromfenac.

3. **Study 792A-302-NZ** (Postoperative Orthopedic pain)
By protocol, this is a standard randomized, placebo controlled, parallel group, double-blind, single-investigator pain study. Pain evaluations were made at 0, 1/4, 1/2, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The 5 treatment groups were (1) bromfenac 25mg, (2) bromfenac 50mg, (3) naproxen 550mg, (4) ketorolac 30mg, and (5) placebo. It was planned that the investigator (Brown) recruit 200 patients. A total of 214 patients was analyzed for efficacy.

The applicant concluded, among other things, Vol. 1.285, page 79, that bromfenac 2 5mg, bromfenac 5 0mg, naproxen, and ketorolac were statistically more effective than placebo from hours 2 through 4. At hour 5, all except bromfenac 25mg were more effective than placebo.

These data provide statistical evidence of the effectiveness of bromfenac 25mg and 50mg.

4. **Study 792A-306-US** (Postoperative Gynecological pain)
By protocol, the acute phase of this study is a standard randomized, placebo controlled, parallel group, double-blind, two-investigator site pain study. Pain evaluations were made at 0, 1/4, 1/2, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The 5 treatment groups were (1) bromfenac 50mg, (2) bromfenac 100mg, (3) ibuprofen -400mg, (4) acetaminophen 650mg/oxycodone 10mg, and (5) placebo. It was planned to recruit a total of 250 patients. A total of 236 patients was analyzed for efficacy.

The applicant concluded, among other things, Vol. 1.291, page 65, that bromfenac 50mg, and 100mg were statistically more effective than placebo from hours 2 through 8. Bromfenac 50mg, and 100mg also had statistically significantly longer times to remedication.

My own analyses show that 50 mg bromfenac is effective. However, in a memorandum from Matthew Thomas, MD dated 12/12/95, DSI recommended that study site 792A-306 not be used to support any efficacy and safety claims for Bromfenac Sodium Capsules. Therefore, the statistical evidence of efficacy for 50mg bromfenac is invalidated for this study site.

III. Adverse Drug Findings: Dr. Widmark was particularly interested in elevated liver enzymes associated with taking bromfenac and the amount of time it took to attain SGPT levels that were higher than the conventional upper limit of normal SGPT.

In a fax dated 9/19/95 to Dr. Widmark, Wyeth provided life table analyses and some patient data regarding "the time to the first elevation of SGPT to at least 1.2 times, 3.0 times, or 8 times the upper limit of normal" for the bromfenac patients in arthritis studies 303, 305, and 309.

The data provided on paper by Wyeth involved only those patients with a SGPT ratio of at least 1.2 times normal. For purposes of statistical analysis, these data are very limited. Therefore any conclusions I draw here are equally limited. I hand entered this data into my computer and looked at this data in a somewhat different way than Wyeth. My approach involved considering 3 patient groups defined by $1.2 \leq SGPT < 2.0$, $2.0 \leq SGPT < 3.0$, and $3 \leq SGPT$. The conditional median time to maximum elevation ratio and the first observation time of maximum elevation are given below.

	No. of Days to Occurrence	
SGPT Group	Earliest	Median
$1.2 \leq SGPT < 2.0$	7	61
$2.0 \leq SGPT < 3.0$	9	53
$3.0 \leq SGPT$	29	70
Overall	7	60

I would conclude from the table above that some bromfenac arthritis patients can be expected to have abnormally elevated SGPT levels after 10 days. The median time to peak level occurs roughly within 2 months after starting bromfenac.

IV. Analytical Issues Related to Efficacy: These Issues involve the estimation of time-to-remedication, the estimation of time-to-onset, the method of data extrapolation, the elimination of patient data from analyses, and claims of comparability.

A. The Estimation of Time-to-Remedication

Wyeth has estimated times-to-remedication by computing mean remedication times over patients randomized to each treatment group. This reviewer believes that for time to event data such as time-to-remedication, median times better summarize estimates of patient experience than means. The following table provides those estimates for the previous and postoperative pain studies. For each drug tested, the far right hand column gives across study median remedication times in ascending order.

Bromfenac NDA 20-535: Median Times to Remedication (Hrs:Min)

							Post Operative Pain				
	AHR-02	AHR-16	AHR-22	792A-301	792A-1.311	792A-3.311	AHR-05	AHR-20	792A-302	792A-306	Median
Placebo	1:44	2:10	1:59	2:00	2:03	2:10	2:34		1:42	2:28	2:03
Aspirin 650 mg	2:40	3:17	3:25								3:17
Ketorolac 30 mg									3:30		3:30
Ibuprofen 200 mg								4:05			4:05
APAP 650/Oxy 10										4:09	4:09
APAP 1000 mg							4:10				4:10
Bromfenac 5 mg	>6:00	3:42			3:50		4:35				4:12
Bromfenac 10 mg		3:43	4:21				5:10				4:21
Nap 550				6:01					2:43		4:24
Ibuprofen 400 mg		5:24	5:47					5:25		3:03	5:25
Bromfenac 50 mg	>6:00		7:03	6:23	5:57	>8:00		>6:00	3:00	4:39	6:09
Bromfenac 25 mg	>6:00	6:25	6:28	6:07	6:05	>8:00	>8:00	>6:00	2:18		6:18
Bromfenac 100 mg			>8:00		>8:00			>6:00		6:03	>8:00
Bromfenac 200 mg					>8:00						>8:00

In study 792A-311, part 3.311 was in fed patients with the exception that there was a fed and a fasted 25 mg bromfenac treatment group. Since the median time to remedication for both the fed and fasted treatment groups exceeded 8-hours, just the single entry, ">8:00", was made for these two 25 mg treatment groups.

In terms of time-to-remedication, dental studies AHR-02, AHR-22, AHR-301, and 792A-311 in fasting patients all show bromfenac 25 and 50 mg have statistically longer times to remedication than placebo. In post-operative pain, only study AHR-05 shows 25mg bromfenac to have a longer time-to-remedication than placebo. Studies 792A-302 and 792A-306 show 50mg bromfenac to have a longer time-to-remedication than placebo.

B. The Estimation of Time-to-Onset of Pain Relief

Time-to-Onset in minutes was estimated by the equation $\frac{30}{\text{LSMEAN\_PRID(30)}}$. This method has drawbacks, but is used when there are no stopwatch data to measure onset. The following table provides these computed estimates for the previous dental and postoperative pain studies.

NDA 20-535: Minutes to Onset of Relief from Pain

							Post Operative Pain				
	AHR-02	AHR-16 *	AHR-22 *	792A-301	792A-1.311	792A-3.311	AHR-05	AHR-20	792A-302	792A-306	Median
Placebo	22			73	77	56	28		20	32	32
Aspirin 650 mg	16										16
Ketorolac 30 mg									21		21
Ibuprofen 200 mg								20			20
APAP 650/Oxy 10										28	28
APAP 1000 mg							16				16
Bromfenac 5 mg	14				31		22				22
Bromfenac 10 mg							20				20
Nap 550				24					20		22
Ibuprofen 400 mg								16		46	31
Bromfenac 25 mg	13			21	30	42	24	30	22		24
Bromfenac 50 mg	13			19	27	50		25	17	33	25
Bromfenac 100 mg					20			21		34	21
Bromfenac 200 mg					19						19

* Study has no 30 minute pain evaluation

C. The Method of Data Extrapolation

Extrapolation is used when a patient has remedicated. In this case, there is no recorded data at the subsequent scheduled evaluation times.

Three methods of extrapolating Pain Relief and Pain Intensity scale data are commonly seen. These are identified by the acronyms BOCF, LOCF and WOCF, which stand respectively for "Baseline Observation Carried Forward", "Last Observation Carried Forward", and "Worst of last and baseline Observation Carried Forward".

At present, there is insufficient empirical data for choosing a preferred extrapolation method. Before making such a decision, we need simply to compare these procedures in a straight forward fashion without feeling obligated to make choices. For a specific primary efficacy variable, major questions are: (1) Within each treatment group, how do these 3 extrapolation procedures and the Raw Data compare from one evaluation time to the next? and (2) How do the dose-response relationships compare across evaluation times for each extrapolation procedure and for the Raw Data. The graphs corresponding to these two comparisons are found in the appendix. These are based on the PRID defined as: PRID = Pain Relief + Pain Intensity Difference.

Based on the Figures in Appendix 1:

1. No matter which drug group is examined and independently of evaluation time, when the adjusted means (LSmeans) are considered, the corresponding PRID scores are rank ordered from lowest to highest as WOCF, BOCF, LOCF, and Raw Data. Furthermore, the WOCF profile and the BOCF profiles are relatively quite similar. The Raw Data are increasingly divergent from the WOCF, BOCF and LOCF extrapolation procedures as drug dose decreases, i.e., as drug efficacy improves, i.e., as patients wait longer to remedicate.
2. The BOCF, LOCF, and WOCF procedures all show good dose response relationships, with little reason to prefer one of these extrapolation procedures over the other. The dose response relationship is much less clear for the Raw Data that for any of the 3 extrapolation procedures.

We have observed here what we already believe. Comparing drugs using extrapolated data is more stable and well ordered than when the Raw Data are analyzed. I see no strong reason to prefer one extrapolation procedure over the other.

D. Pain Scores at Remedication

Study AHR-22 in a particularly interesting study because it involves four doses of bromfenac as well as a placebo. This study shows a bromfenac dose-response relationship. From raw data, which is not provided here, it is clear those patients on high doses of Bromfenac remedicate/dropout at notably higher PRID scores than placebo and low-dose Bromfenac patients. This is summarized in the following table.

Drug	Median PRID @ Remedication
Placebo	0
Brom 10 mg	1
Brom 25 mg	1
Brom 50 mg	1.5
Brom 100 mg	3

The reason for this unusual patient behavior, i.e., asking for rescue medication when pain levels are not particularly high is unknown. The investigator for study AHR-22 excluded such patients from his published pain scale analyses. Wyeth did not make these exclusions and applied an intent-to-treat approach. This latter approach tends less to disturb the original randomization of patients to treatment groups.

E. Comparability Claims

I know of no statistical methods for asserting the comparability of two analgesics. The complications associated statistical assertions of comparability include (1) The pain scales are inherently not numeric. The assignment of "fictitious" numbers to pain categories or the use of a visual analog scale does not negate the fact that it is no simple matter to assign a value to how close the expected values of the data for two analgesics must be to assert that comparability exists, (2) Some analgesics have slower onset and longer duration of action than others. Any definition of comparability must also take this fact into account, (3) Some studies have rather large placebo effects, which gives these studies little up-side sensitivity, (4) Even if the pain curves for two analgesics were identical, say over a 6-hour evaluation period, should the true

remedication patterns be sufficiently different, there would seem to be little foundation for claiming comparability. In my opinion, statements of comparability of analgesic effect essentially constitute a medical overview evaluation for which I have no formal statistical basis.

4. Conclusions

A. In . Pain, the applicant has shown the statistical effectiveness of bromfenac 25 and 50 mg in studies AHR-02, AHR-22, and 792A-301. Additionally bromfenac 25mg was shown effective in study AHR-16.

B. In Postoperative Pain, the applicant has shown the statistical effectiveness of bromfenac 25mg in studies AHR-05 and 792A-302.

Bromfenac 50mg was shown statistically effective in study 792A-302. However, in a memorandum from Matthew Thomas, MD dated 12/12/95, DSI recommended that study site 792A-306 not be used to support any efficacy and safety claims for Bromfenac Sodium Capsules. Therefore, for this reason, the statistical evidence of efficacy found in post operative surgery for 50mg bromfenac is considered invalidated.

Richard A. Stein

Richard A. Stein, Ph.D.
Mathematical Statistician

Team Leader:

Ralph Harkins, Ph.D. 12/18/95

Hoi M. Leung, PhD

APPEARS THIS WAY
ON ORIGINAL

CC: Original NDA 20-535 .
HFD-550/John Hyde, PhD, M.D.
HFD-550/Rudolph Widmark, M.D., PhD
HFD-701/ Charles Anello, DSc
HFD-725/Ralph Harkins, PhD
HFD-550/Chin Koerner, CSO
HFD-550/Div. File

APPEARS THIS WAY
ON ORIGINAL

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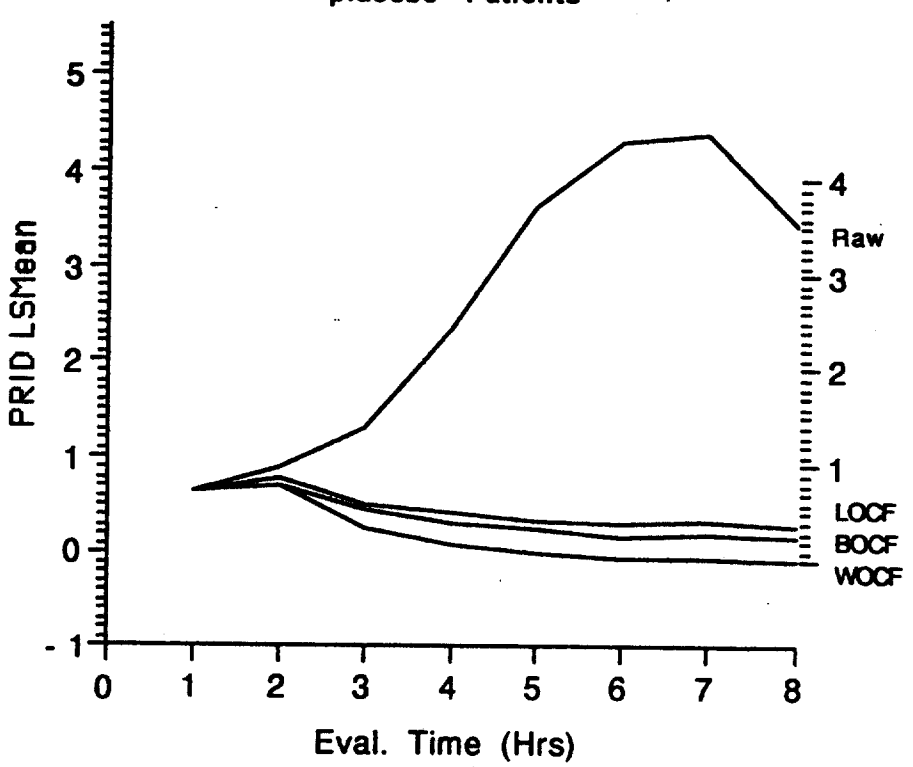
ON ORIGINAL

Appendix

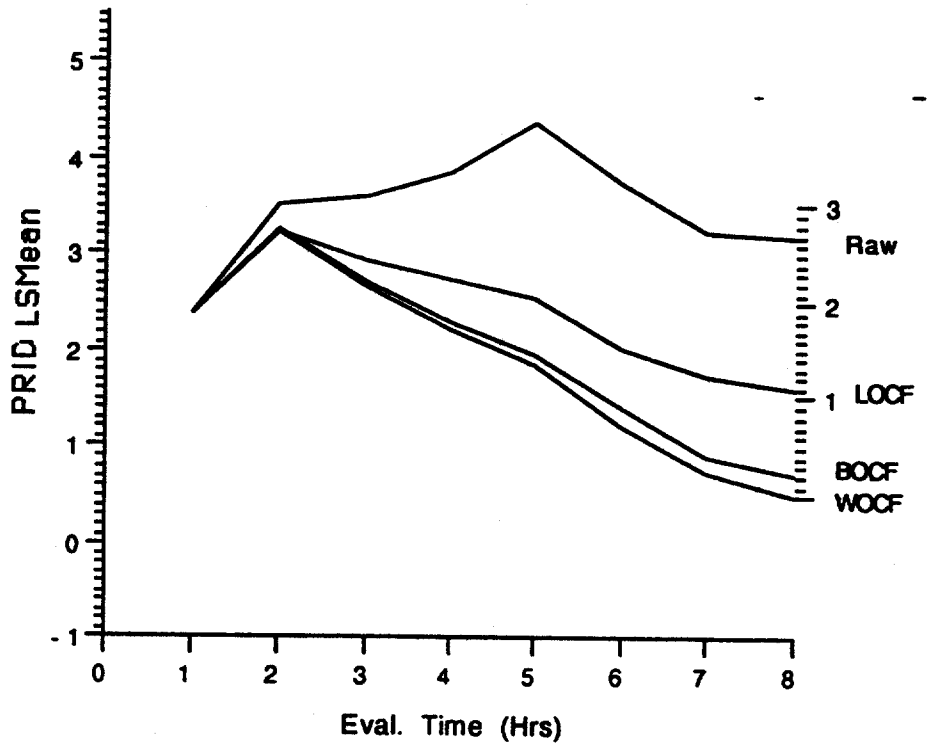
Appendix 1: Comparisons of BOCF, LOCF, WOCF and Raw Data Pain Profiles

Bromfenac Study AHR-22
Comparison of Data Extrapolation Methods used when Patients Remedicate
LSMeans are based on the Model:
PRID = μ + Trt[i] + β*PI[0] + error

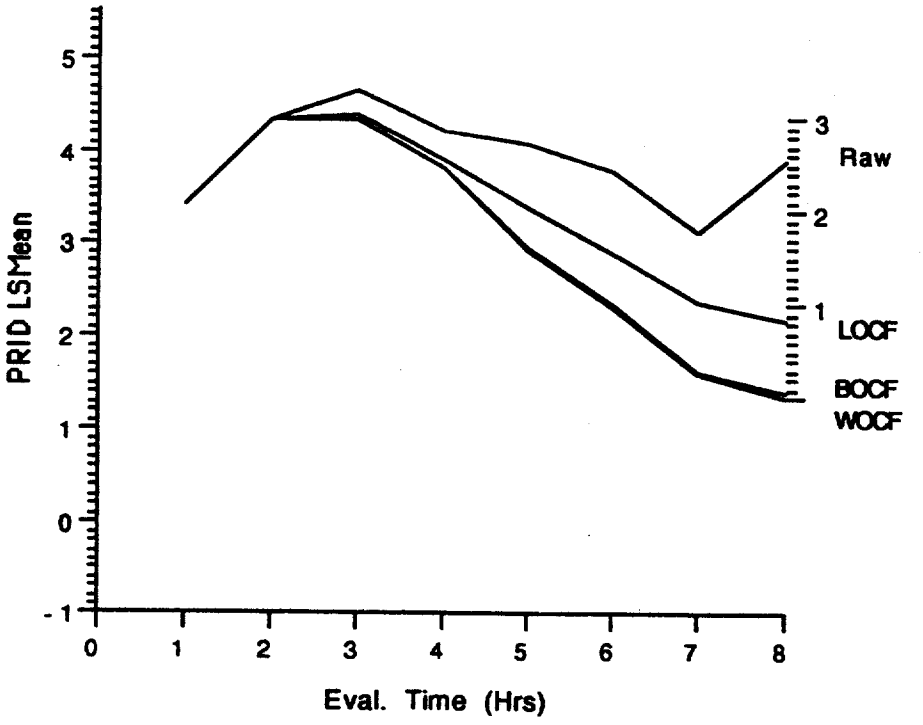


Raw: No extrapolated or imputed patient data
LOCF: Last recorded Observation value Carried Forward
BOCF: Baseline Observation Carried Forward
WOCF: Worst of baseline or last Observation Carried Forward

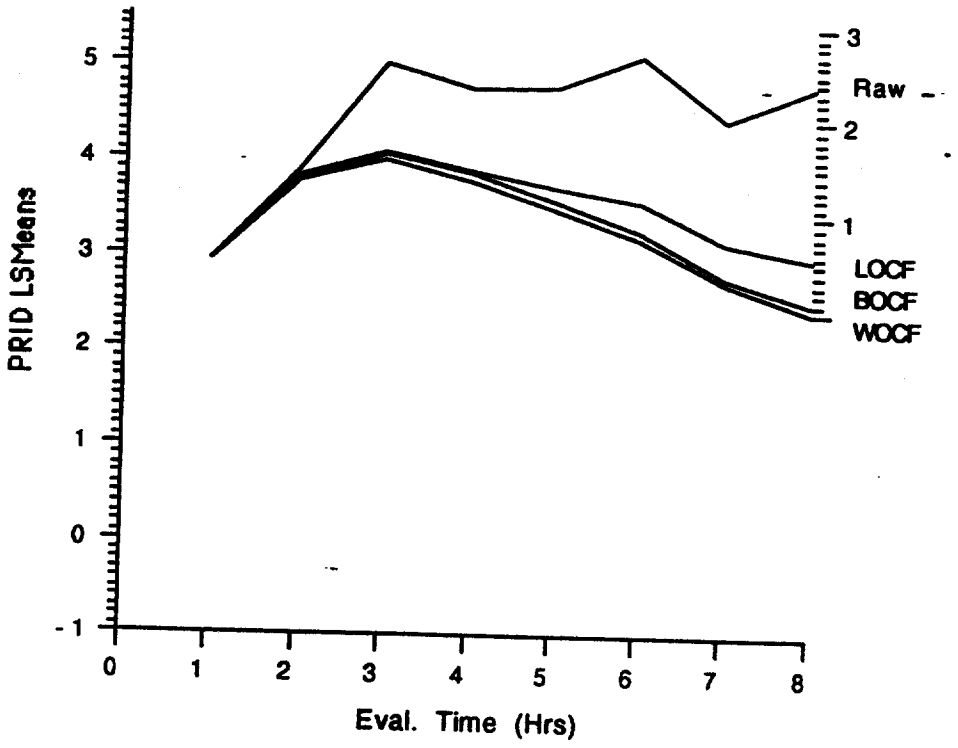
Bromfenac 10 mg Patients



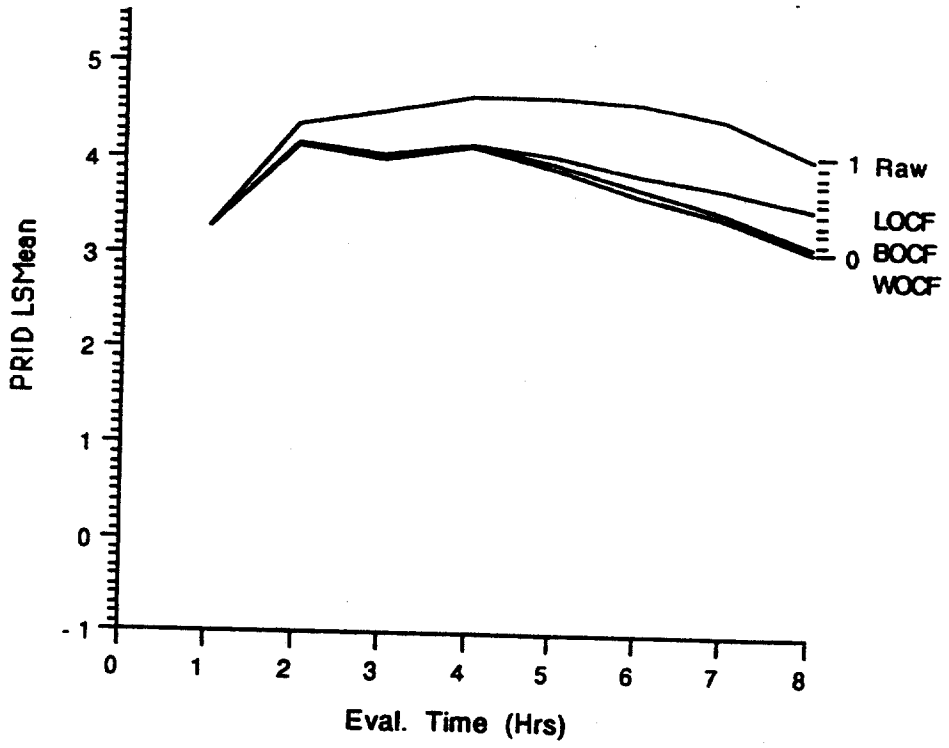
Bromfenac 25 mg Patients



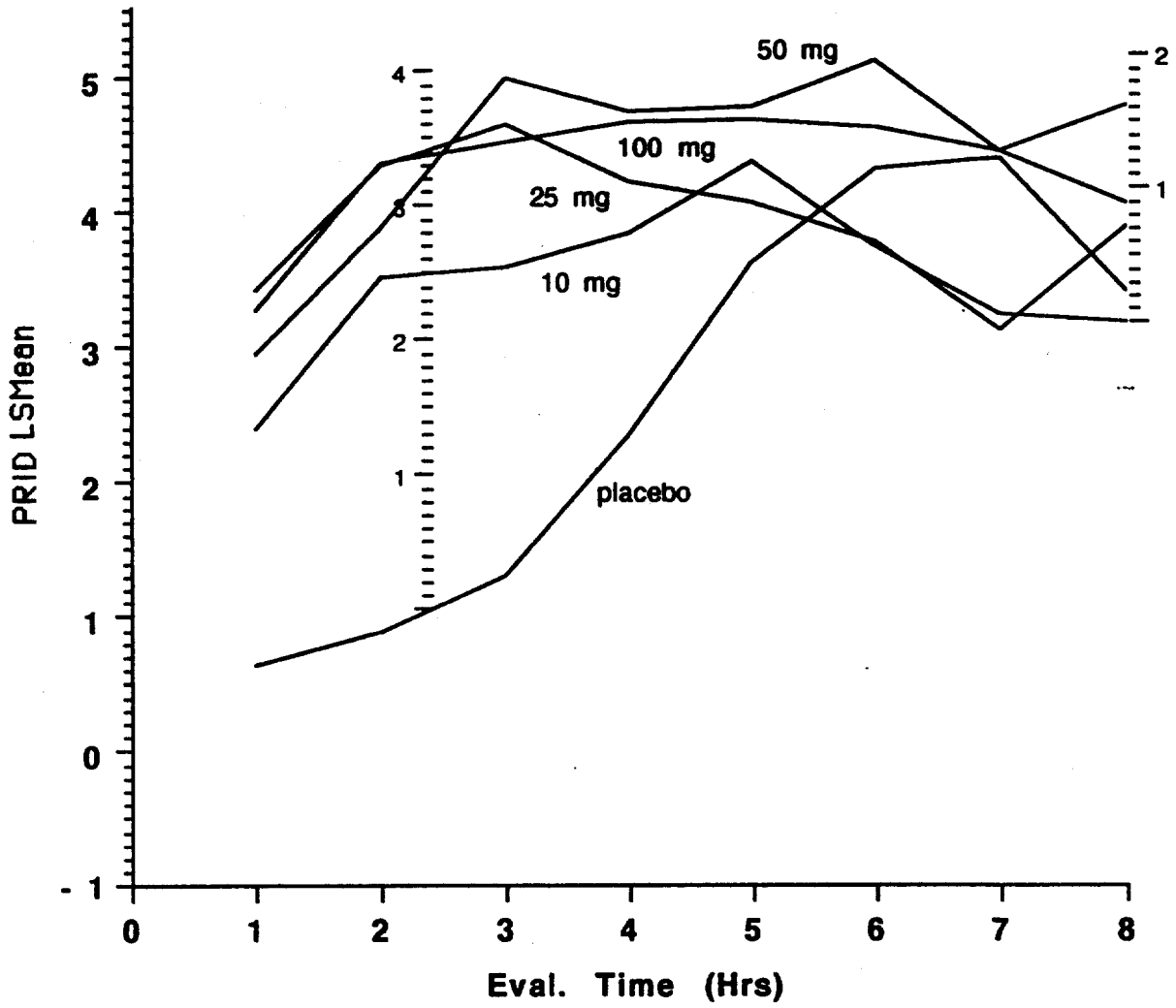
Bromfenac 50 mg Patients



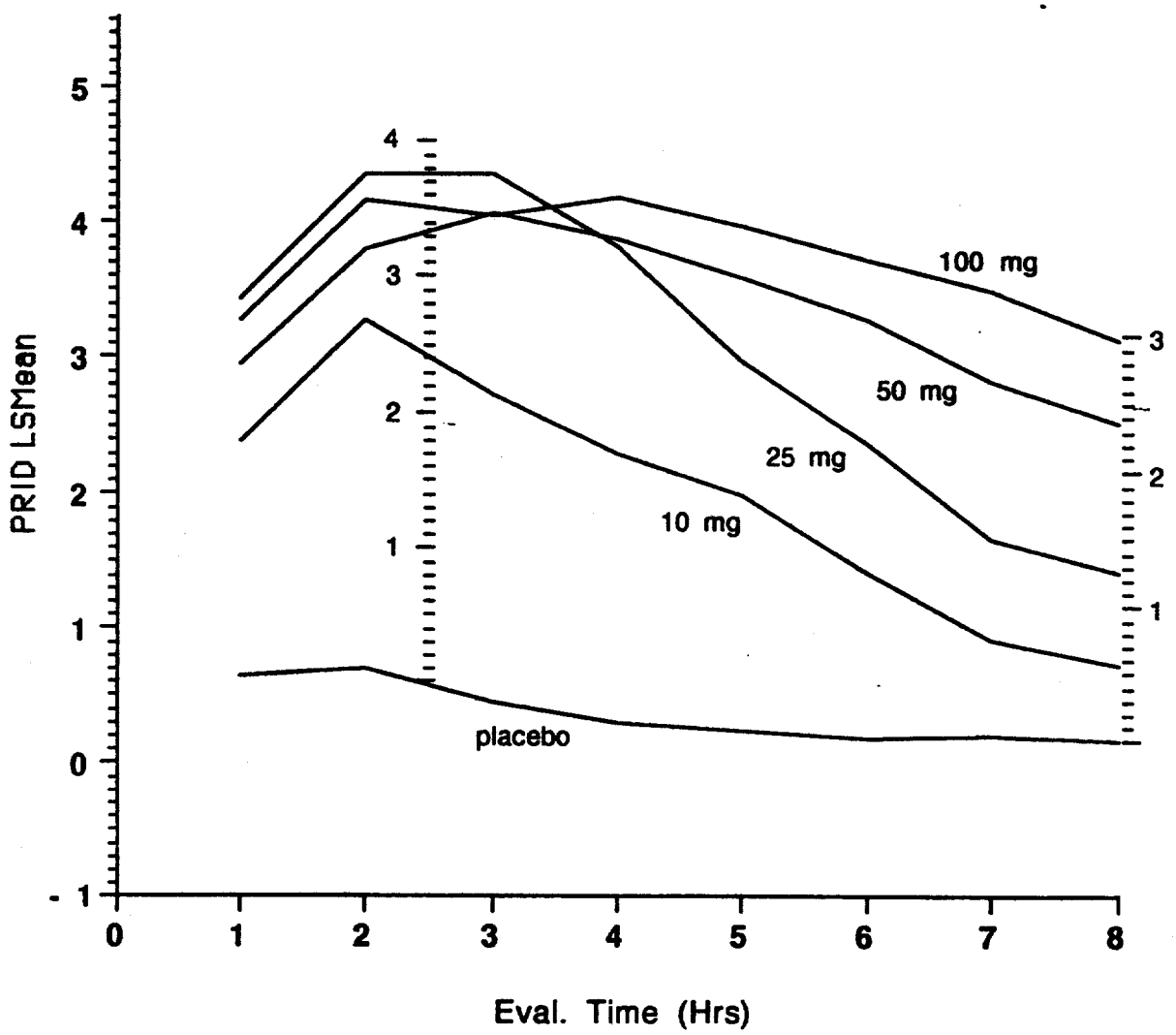
Bromfenac 100 mg Patients



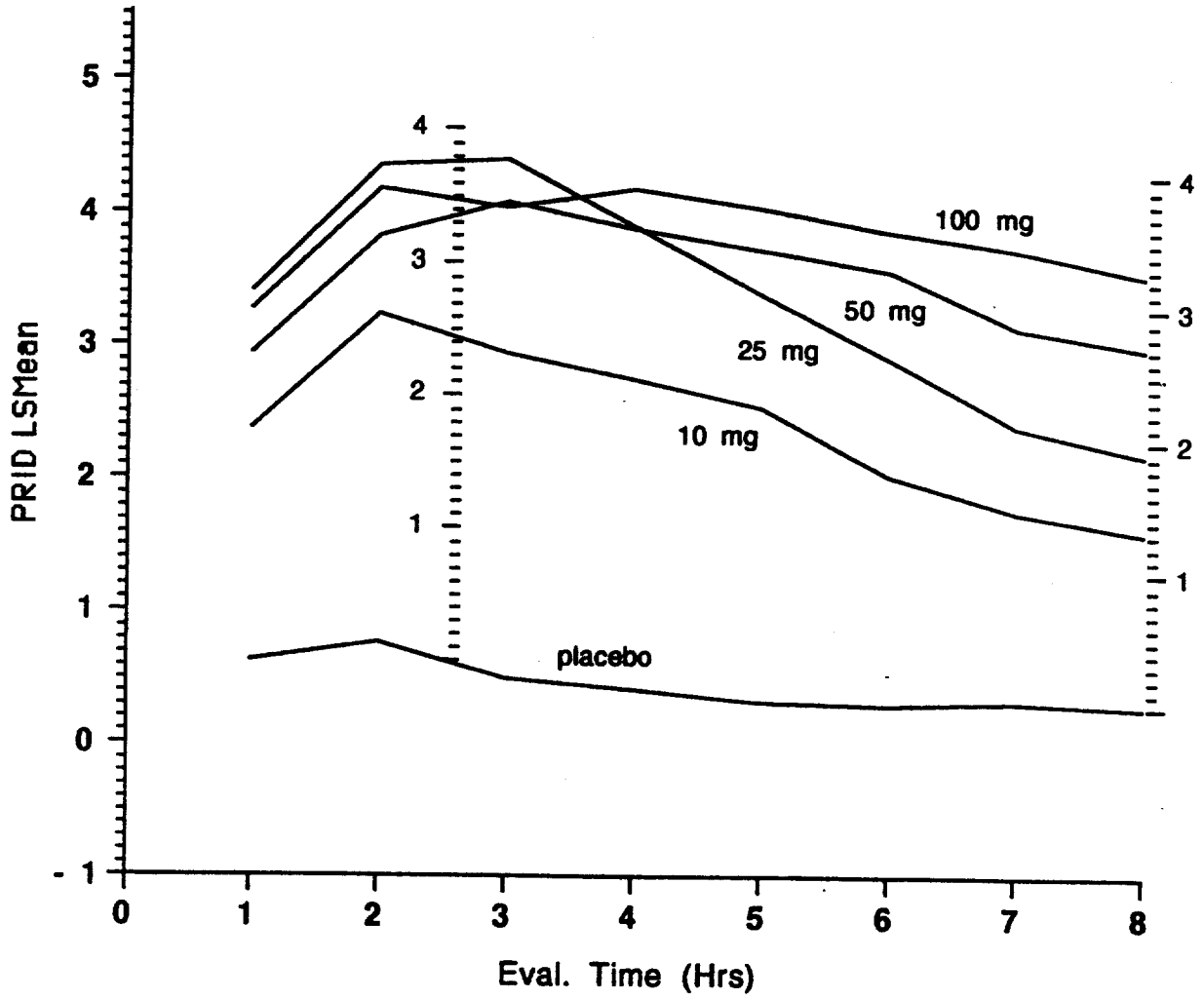
Study AHR-22 Raw Data Dose Comparisons



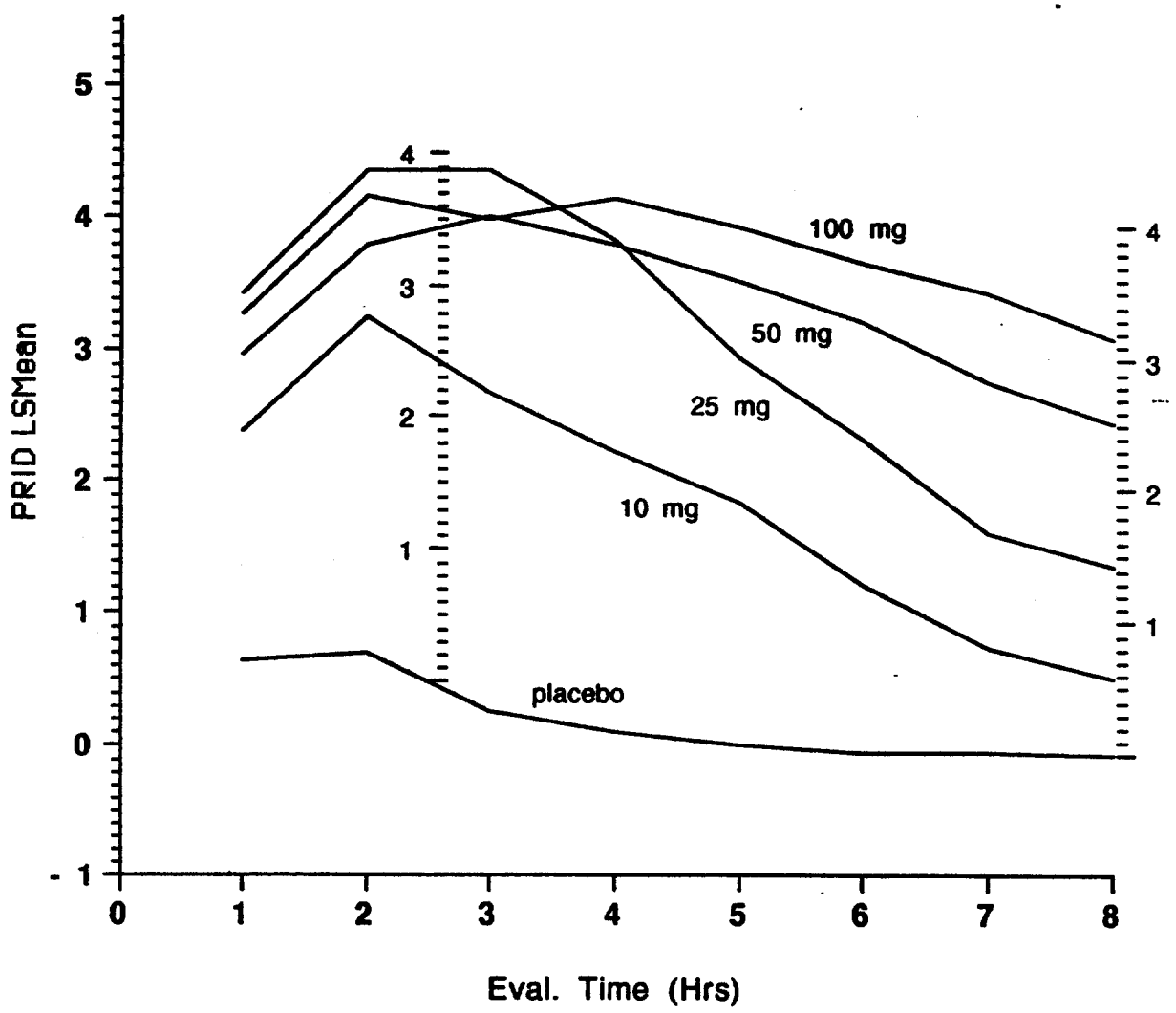
Study AHR-22 BOCF Dose Comparisons



Study AHR-22 LOCF Dose Comparisons



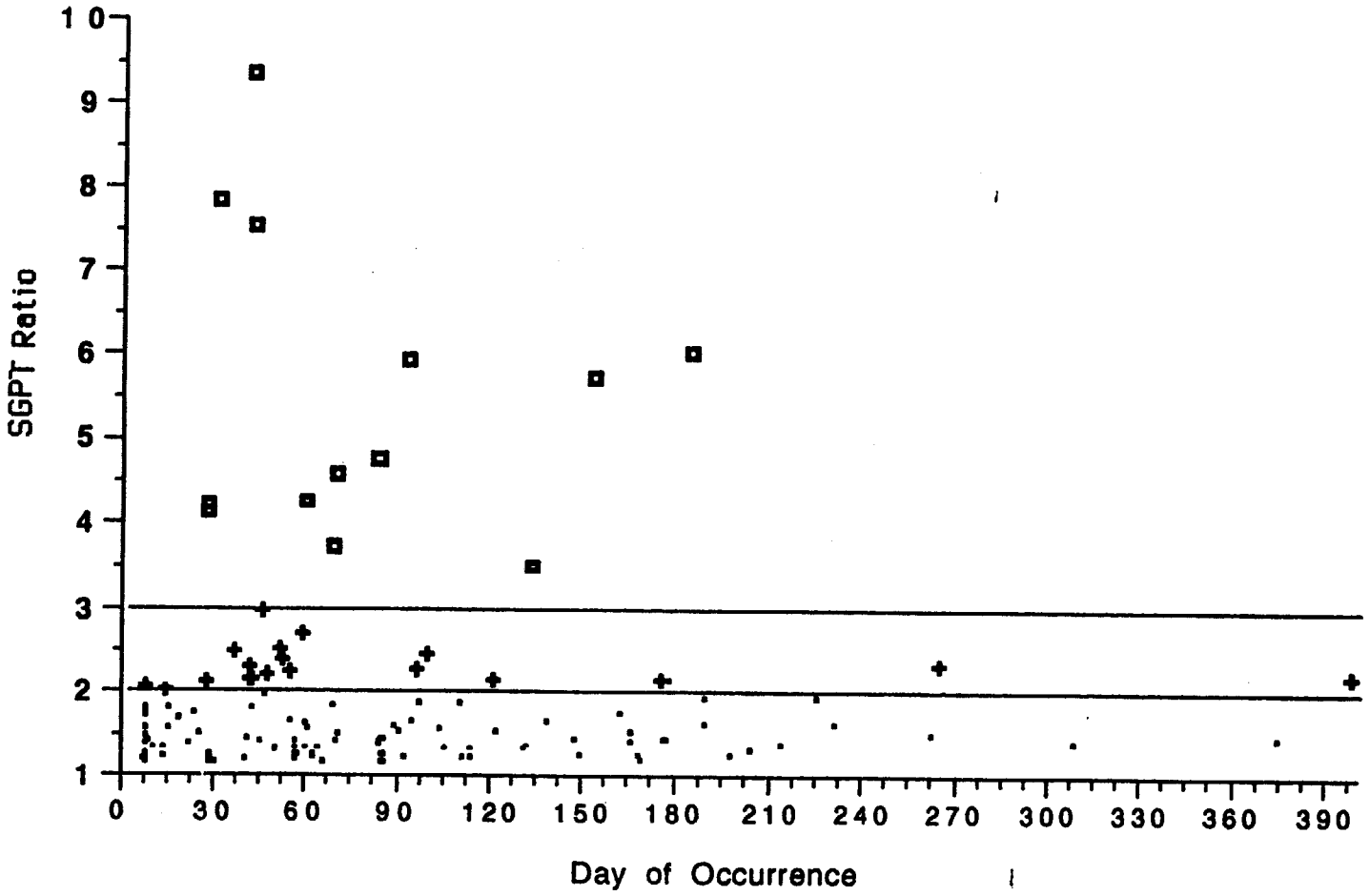
Study AHR-22 WOCF Dose Comparisons



Appendix 2: Elevated Liver Function in Studies 303, 305, 309

In a fax dated 9/19/95 to Dr. Widmark, FDA, Wyeth provided patient data of "time to the first elevation of SGPT to at least 1.2 times, 3.0 times, or 8 times the upper limit of normal" for the bromfenac patients in arthritis studies 303, 305, and 309.

The data provided on paper by Wyeth involved only those patients with a SGPT ratio (= observed maximum SGPT/Upper limit of Normal SGPT)of at least 1.2 times normal. The conditional median time to maximum elevation ratio and the first observation time of maximum elevation are given below.



Appendix 3: Analysis of Analgesic Data / an Alternate Attempt

The analysis of Pain Relief (PR) and Pain Intensity (PI) scale data is hampered by the fact that time to patient remedication is treatment dependent. First dose pain data become unavailable (missing) after a patient remedicates. In this reviewer's opinion, missing data are an ever increasing source of bias in the analysis PR and PI data at later evaluation times. This bias is cumulative for the TOTPAR and the SPID which are essentially defined as areas under the PR and PI curves. It is unclear whether the BOCF, LOCF, or WOCF extrapolation procedures can compensate for bias.

An alternate approach resembles the use of straight line random regression. Pain Relief was chosen because lack of a baseline value would seem to be simpler to deal with initially. In this case, each patient's PR data could be fitted by an appropriate equation. The choice of equation is important. Individual patient PR curves look considerably like blood concentration curves that commonly have the mathematical form:

$$PR(t) = \mu_o\left[e^{-\mu_e(t-\tau)} - e^{-\mu_a(t-\tau)}\right] \qquad (1)$$

Here μ_o, μ_e, μ_a, and τ are constants to be determined which provide the best fit of the curve to the data. It is known that fitting this equation is an awkward task when $\mu_e \approx \mu_a$. In addition, my current experience is that commonly, not enough pain data are collected on the rising part of the PR curve to allow good estimates of the parameters of equation (1). In fact, the JMP software I have been using too often fails to converge to a solution at all.

Another functional form that has some promise, but which I have barely examined is:

$$PR(t) = \mu_o\left[(1+t)^{-\mu_e} - (1+t)^{-\mu_a}\right] \qquad (2)$$

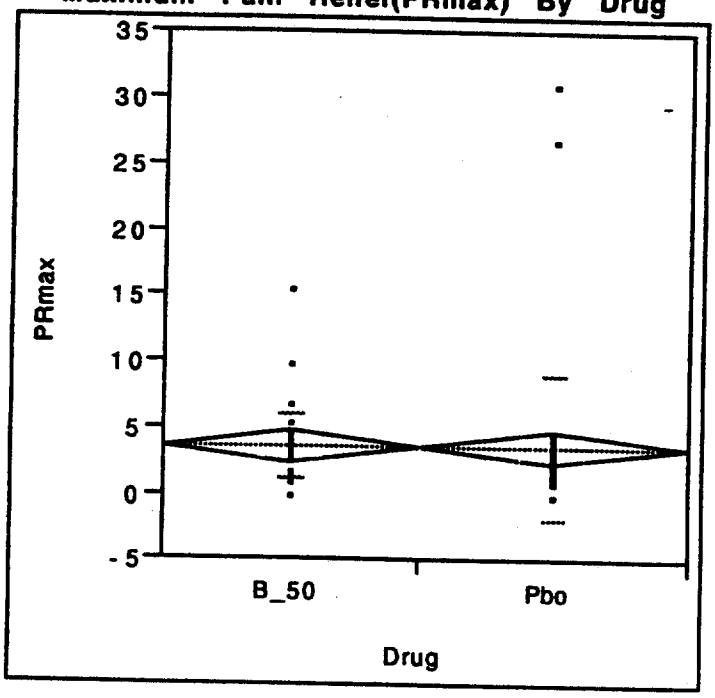
A more "user friendly" functional form is to use the equation

$$PR(t) = PR_{\max}\left[\frac{t}{T_{\max}} e^{\left(1-\frac{t}{T_{\max}}\right)}\right]^{\beta} \qquad (3)$$

Here the fitted parameters of interest, PR_{max}, T_{max}, and β can be calculated directly by JMP software for each patient. I have chosen only the bromfenac 50 mg and placebo data from study 792A-306 for a by-patient variance unweighted statistical analysis of each of these 3 parameters. The results, which follow are lackluster.

1. For 17/93 patients (18%), there were complications in estimating PR_{max}, T_{max}, and β.
2. The parameter estimates data obtained within treatment groups seem to be ill distributed.
3. Statistically superior pain relief for 50 mg bromfenac over placebo is not clearly shown.
4. The time to maximum pain relief is statistically significantly longer for bromfenac than for placebo.

Maximum Pain Relief(PRmax) By Drug



One Way Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	0.1446	0.1446	0.0076
Error	91	1735.1619	19.0677	Prob>F
C Total	92	1735.3065		0.9308

Means for One-way ANOVA

Level	Number	Mean	Std Error
B_50	46	3.51304	0.64383
Pbo	47	3.59191	0.63694

Tests that the Variances are Equal

Test	F Ratio	DF Num.	DF Den	Prob>F
O'Brien[.5]	1.4084	1	91	0.2384
Brown-Forsythe	0.4883	1	91	0.4864
Levene	1.1133	1	91	0.2942
Bartlett	24.1201	1	.	0.0000

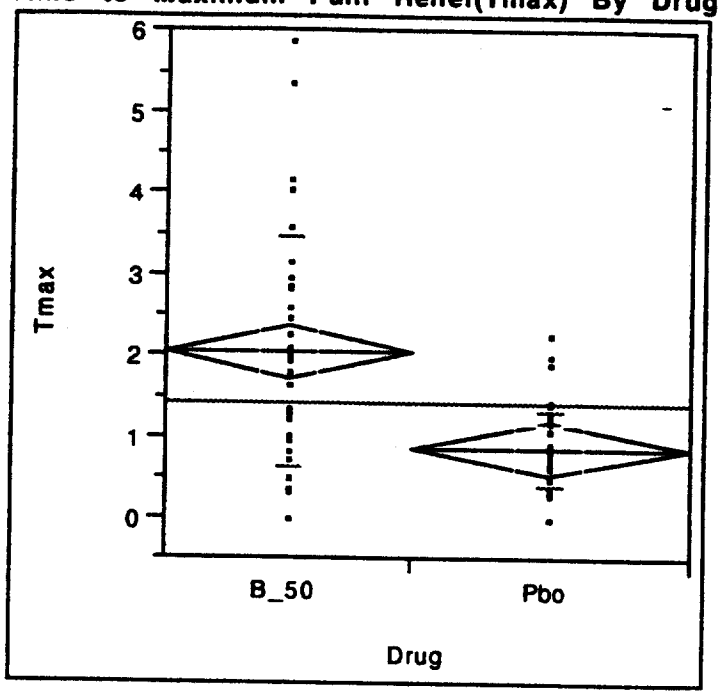
Welch ANOVA testing Means Equal, allowing Std's Not Equal

F Ratio	DF Num.	DF Den	Prob>F
0.0077	1	65.257	0.9304

Wilcoxon / Kruskal-Wallis Tests (Rank Sums)

ChiSquare	DF	Prob>ChiSq
5.3801	1	0.0204

Time to Maximum Pain Relief(Tmax) By Drug



One Way Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	27.75485	27.7549	25.5268
Error	74	80.45909	1.0873	Prob>F
C Total	75	108.21394		0.0000

Means for One-way ANOVA

Level	Number	Mean	Std Error
B_50	36	2.06056	0.17379
Pbo	40	0.85025	0.16487

Tests that the Variances are Equal

Test	F Ratio	DF Num.	DF Den	Prob>F
O'Brien[.5]	12.5037	1	74	0.0007
Brown-Forsythe	21.5067	1	74	0.0000
Levene	21.8127	1	74	0.0000
Bartlett	36.6946	1	.	0.0000

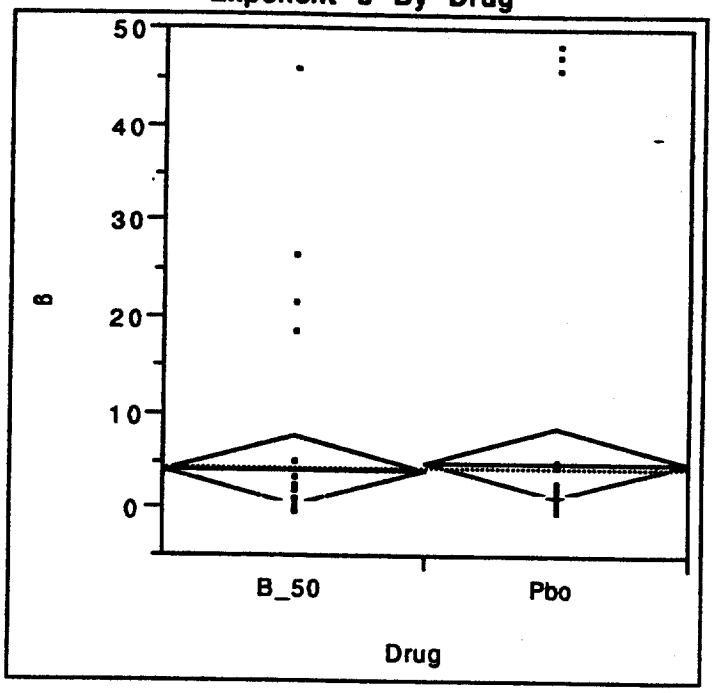
Welch ANOVA testing Means Equal, allowing Std's Not Equal

F Ratio	DF Num.	DF Den	Prob>F
23.4622	1	42.373	0.0000

Wilcoxon / Kruskal-Wallis Tests (Rank Sums)

ChiSquare	DF	Prob>ChiSq
17.2359	1	0.0000

Exponent 8 By Drug



One Way Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	16.8677	16.868	0.1343
Error	72	9044.6744	125.620	Prob>F
C Total	73	9061.5421		0.7151

Means for One-way ANOVA

Level	Number	Mean	Std Error
B_50	37	3.89405	1.8426
Pbo	37	4.84892	1.8426

Tests that the Variances are Equal

Test	F Ratio	DF Num.	DF Den	Prob>F
O'Brien[.5]	0.6139	1	72	0.4359
Brown-Forsythe	0.1098	1	72	0.7413
Levene	0.5399	1	72	0.4649
Bartlett	3.5657	1	.	0.0590

Welch ANOVA testing Means Equal, allowing Std's Not Equal

F Ratio	DF Num.	DF Den	Prob>F
0.1343	1	65.721	0.7152

Wilcoxon / Kruskal-Wallis Tests (Rank Sums)

ChiSquare	DF	Prob>ChiSq
0.5019	1	0.4787