CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-754

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Ketorolac **ANDA #:** 74-754 ....
SPONSOR: Lemmon
DOSAGE FORM: Tablet **STRENGTH:** 10 mg
TYPE OF STUDY: Single dose, fasting and single dose non-fasting.
STUDY SITE:
CLINICAL: Gateway Medical Research, St. Charles, MO
ANALYTICAL: Bioassay Laboratories, Houston, TX.

NOT A FIRST GENERIC

STUDY SUMMARY

Fasting Study: This was a 2-way cross-over, fasting, in 26 subjects with no alternates. All subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in 3 subjects, all on the reference formulation (#3, 10, and 24). No therapy was required.
90% C.I. limits on $LAUC_t$ (92.3% - 102%), $LAUC_{inf}$ (92.9% - 102%) and LC_{max} (90.6% - 112%) are within acceptable ranges.

Non Fasting Study: This was a three way, single dose food effect study in 18 subjects with no alternates. Of 18 subjects enrolled in the study, subj #5 withdrew prior to Period 3 due to family situation, #15 failed to show up for phase II dosing for personal reasons. Total number of subjects completing the study was 16. After the assay, the firm noticed that, for subject #9, there were problems with interference in the chromatograms. Thus no valid data can be obtained from this subject. For this nonfasting study, the number of subjects used in the statistical analysis was 15. The ratios of LSQ means for $LAUC_t$ (96%), $LAUC_{inf}$ (96.2%) and LC_{max} (90.5%) are within the acceptable limits.

Dissolution: The test tablet meets the dissolution specifications as follows:
USP XXIII, Paddle, 50 RPM
Medium: Water at 37°C, 600 ml.
Specification: NLT

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. **BRANCH:** II
INITIAL: /S/ **DATE:** 9-17-96

TEAM LEADER: Shrinivas Nerurkar, Ph.D. **BRANCH:** II
INITIAL: /S/ **DATE:** 9-27-1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith K. Chan, Ph.D.
INITIAL: /S/ **DATE:** 9/27/96

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: /S/ **DATE:**

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Ketorolac **ANDA #:** 74-754 ....
SPONSOR: Lemmon
DOSAGE FORM: Tablet **STRENGTH:** 10 mg
TYPE OF STUDY: Single dose, fasting and single dose non-fasting.
STUDY SITE:
CLINICAL:
ANALYTICAL:

[redacted] A FIRST GENERIC

STUDY SUMMARY

Fasting Study: This was a 2-way cross-over, fasting, in 26 subjects with no alternates. All subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in 3 subjects, all on the reference formulation (#3, 10, and 24). No therapy was required.
90% C.I. limits on $LAUC_t$ (92.3% - 102%), $LAUC_{inf}$ (92.9% - 102%) and LC_{max} (90.6% - 112%) are within acceptable ranges.

Non Fasting Study: This was a three way, single dose food effect study in 18 subjects with no alternates. Of 18 subjects enrolled in the study, subj #5 withdrew prior to Period 3 due to family situation, #15 failed to show up for phase II dosing for personal reasons. Total number of subjects completing the study was 16. After the assay, the firm noticed that, for subject #9, there were problems with interference in the chromatograms. Thus no valid data can be obtained from this subject. For this nonfasting study, the number of subjects used in the statistical analysis was 15. The ratios of LSQ means for $LAUC_t$ (96%), $LAUC_{inf}$ (96.2%) and LC_{max} (90.5%) are within the acceptable limits.

Dissolution: The test tablet meets the dissolution specifications as follows:
USP XXIII, Paddle, 50 RPM
Medium: Water at 37°C, 600 ml.
Specification: NLT 75% in 45 minutes

PRIMARY REVIEWER: Nhan L. Tran, Ph.D. **BRANCH:** II
INITIAL: /S/ **DATE:** 9-17-96

TEAM LEADER: Shrinivas Nerurkar, Ph.D. **BRANCH:** II
INITIAL: /S/ **DATE:** 9-27-1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith K. Chan, Ph.D.
INITIAL: /S/ **DATE:** 9/27/96

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: /S/ 10/28/96

SUMMARY OF PK PARAMETERS:

FASTING STUDY:

	Test	Reference	90% C.I	intra CV	inter CV	Total CV
AUC_{0-t}	6424 ng.ml/hr	6655 ng.ml/hr	92.3%-102%	9.5%	22%	31.5%
$AUC_{0-\infty}$	6722	6943	93%-102%	9.02%	22%	31%
C_{max}	1733 ng/ml	1713 ng/ml	91%-112%	20.1%	27%	47.1%

Statistical Procedure: Appropriate for 2-way cross-over.
Comments: All parameters were within the acceptable 90% C.I limits .

NON FASTING STUDY:

	$Test_{Fed}$	$Reference_{Fed}$	Ratio T/F(geo)	intra CV	inter CV	Total CV
AUC_{0-t}	5992 ng.ml/hr	6266 ng.ml/hr	96.1%	11.8%	26%	37.8%
$AUC_{0-\infty}$	6303	6597	96.2%	11.75%	25%	36.75%
C_{max}	1055 ng/ml	1198 ng/ml	90.5%	23%	25%	48%

Statistical Procedure: Appropriate for 3-way cross-over.
Comments: All parameters were within the acceptable ratio limits .

In-Vitro Dissolution:

USP XXIII Method II (Paddle), 600 ml water, 50 RPM
Specifications:

Waiver Request: None.

Comparison to Past Generic Products: **Parameters are comparable**

DBE STUDY APPROVAL FORM

ANDA #:	**74-754**	**FIRM:**	**Lemmon**	**FIRST GENERIC:**	**NO**
DRUG:	**Ketorolac**	**DOSAGE FORM:**	**Tablet**	**STRENGTH:**	**10mg**
RLD:	**Toradol®**	**FIRM:**	**Syntex**	**BIO REVIEWER:**	**N. Tran**

Therapeutic Category: NSAID Dosage Regimen: Varied
Solubility/Permeability: High solubility/high permeability (Dissolution: NLT minutes and Tmax is less than 1 hour.

FASTING STUDY:
Clinical Procedure:

Center:	C	Principal Inv.:	I.
# of Subjects Planned:	26	# of Subjects Required:	26
# dropped out:	0	# of subject completed:	26
# in data analysis:	26	Subset analysis:	No
Randomization:	Yes	Demographic:	All males, age
Dose administration:	2x10mg	between 18-45, wt: not more than ±15%	
Blood sample:	No deviation was noted	from ideal body weight.	

Safety summary: Minor adverse events such as emesis, diarrhea and light headache were reported during the study for 3 subjects who were on reference formulation: Subj #3, 10, and 24. The symptom was mild and no treatment was required.

NON FASTING STUDY:
Clinical Procedure:

Center:	-	Principal Inv.:	I.
# of Subjects Planned:	18	# of Subjects Required:	18
# dropped out:	2	Reasons:	Failed to return
# of subject completed:	16	# in data analysis:	15 (Samples from
Subset analysis:	N/A	subject #9 were contaminated.	
Randomization:	Yes	Demographic: Same as in fasted study.	
Dose administration:	2x10mg	Blood sample:	No deviation noted

Safety summary: For this study, there was no adverse event reported by any subject.

ANALYTICAL PROCEDURE:

Center: ----- Principal Inv.:
Analytical Method
Pre-study validation: Accuracy:between 97.2%-102% for all QC samples.
Precision: between 0.2%-2.5%, Sensitivity: 20 ng/ml
Stability validation: Stable for 87 days
Within study validation: Accuracy & precision comparable to pre-study data
Standard curve: 20ng/ml-300ng/ml QC Samples: 50, 350, and 2500ng/ml
Comments: Acceptable

PK/STATISTICAL ANALYSIS:

PK Calculation Procedure: Trapezoidal rule for AUCs, Cmax from raw data.
Spot checked data: No discrepancies noted
Mean Plasma Profile: OK
Individual Plasma Profile: Inspected and found acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

DRUG NAME: Ketorolac **ANDA #:** 74-754
SPONSOR: Lemmon
DOSAGE FORM: Tablet **STRENGTH:** 10 mg
TYPE OF STUDY: Single dose, fasting and single dose non-fasting.
STUDY SITE:
CLINICAL:
ANALYTICAL:

NOT A FIRST GENERIC

STUDY SUMMARY

Fasting Study: This was a 2-way cross-over, fasting, in 26 subjects with no alternates. All subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in 3 subjects, all on the reference formulation (#3, 10, and 24). No therapy was required.
90% C.I. limits on $LAUC_t$ (92.3% - 102%), $LAUC_{inf}$ (92.9% - 102%) and LC_{max} (90.6% - 112%) are within acceptable ranges.

Non Fasting Study: This was a three way, single dose food effect study in 18 subjects with no alternates. Of 18 subjects enrolled in the study, subj #5 withdrew prior to Period 3 due to family situation, #15 failed to show up for phase II dosing for personal reasons. Total number of subjects completing the study was 16. After the assay, the firm noticed that, for subject #9, there were problems with interference in the chromatograms. Thus no valid data can be obtained from this subject. For this nonfasting study, the number of subjects used in the statistical analysis was 15. The ratios of LSQ means for $LAUC_t$ (96%), $LAUC_{inf}$ (96.2%) and LC_{max} (90.5%) are within the acceptable limits.

Dissolution: The test tablet meets the dissolution specifications as follows:
USP XXIII, Paddle, 50 RPM
Medium: Water at 37°C, 600 ml.
Specification:

PRIMARY REVIEWER: /S/ Nhan L. Tran, Ph.D. **BRANCH:** II
INITIAL: _____ **DATE:** 9-17-96

TEAM LEADER: /S/ Shrinivas Nerurkar, Ph.D. **BRANCH:** II
INITIAL: _____ **DATE:** 9-27-1996

DIRECTOR, DIVISION OF BIOEQUIVALENCE: /S/ Keith K. Chan, Ph.D.
INITIAL: _____ **DATE:** 9/27/96

DIRECTOR, OFFICE OF GENERIC DRUGS: /S/
INITIAL: _____ **DATE:** _____

In Vitro Dissolution Testing

Drug: Ketorolac Tromethamine, Dose Strength: 10 mg, Tablet
ANDA No.: 74-754, Firm: Lemmon
Submission Date: May 14, 1996
File Name: 74754SD.596

I. Conditions for Dissolution Testing:

USP XXII, Paddle: RPM: 50, 600 ml, Water, No. Units Tested: 12
Specifications:
Reference Drug: TORADOL® 10 mg Tablets by SYNTEX.
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 293-117, Strength: 10 mg			Reference Product Lot # 2541, Strength: 10 mg.		
	Mean %	Range	%CV	Mean %	Range	%CV
15	89.6		13.5	93.5		8.2
30	97.3		7.4	98.1		4.9
45	99.0		5.5	100.3		3.6
60	99.7		4.4	101.3		3.0

Means (N = 15) of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV) (Fast)	Test (%CV) (Fed)	Ref (%CV) (Fed)
AUC_{0-t}	7136.83 (21.88%)	5992.38 (26.05%)	6266.08 (24.37%)
$AUC_{0-\infty}$	7528.05 (22.16%)	6302.95 (25.28%)	6569.65 (23.01%)
C_{max}	1936.60 (21.58%)	1055.20 (24.40%)	1198.47 (25.07%)
T_{max}(h)	0.939 (32.6%)	2.0 (56.7%)	1.94 (58.8%)
$T_{1/2}$(h)	6.16 (19.8%)	5.25 (18.6%)	5.21 (14.19%)

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. From the ANOVA output, least squares means (log transformed data) of the test and reference formulations were obtained and they were used for the estimation of the ratios of test/reference for AUCt, AUCinf, and Cmax. For the log transformed data, this ratio can be estimated as [100xe$^{(LSMtest-LSMreference)}$], with the least-squares mean (LSM) computed by using the LSMEANS statement in the SAS GLM procedure.

Results indicated that, for log transformed parameters, the ratios of the test and reference formulations under nonfasting conditions for ***AUCt (96.0%), AUCinf (96.2%) and Cmax (90.5%), all are within the current acceptable ratio limits of 80% to 125%.***

V. Composition of the test tablets

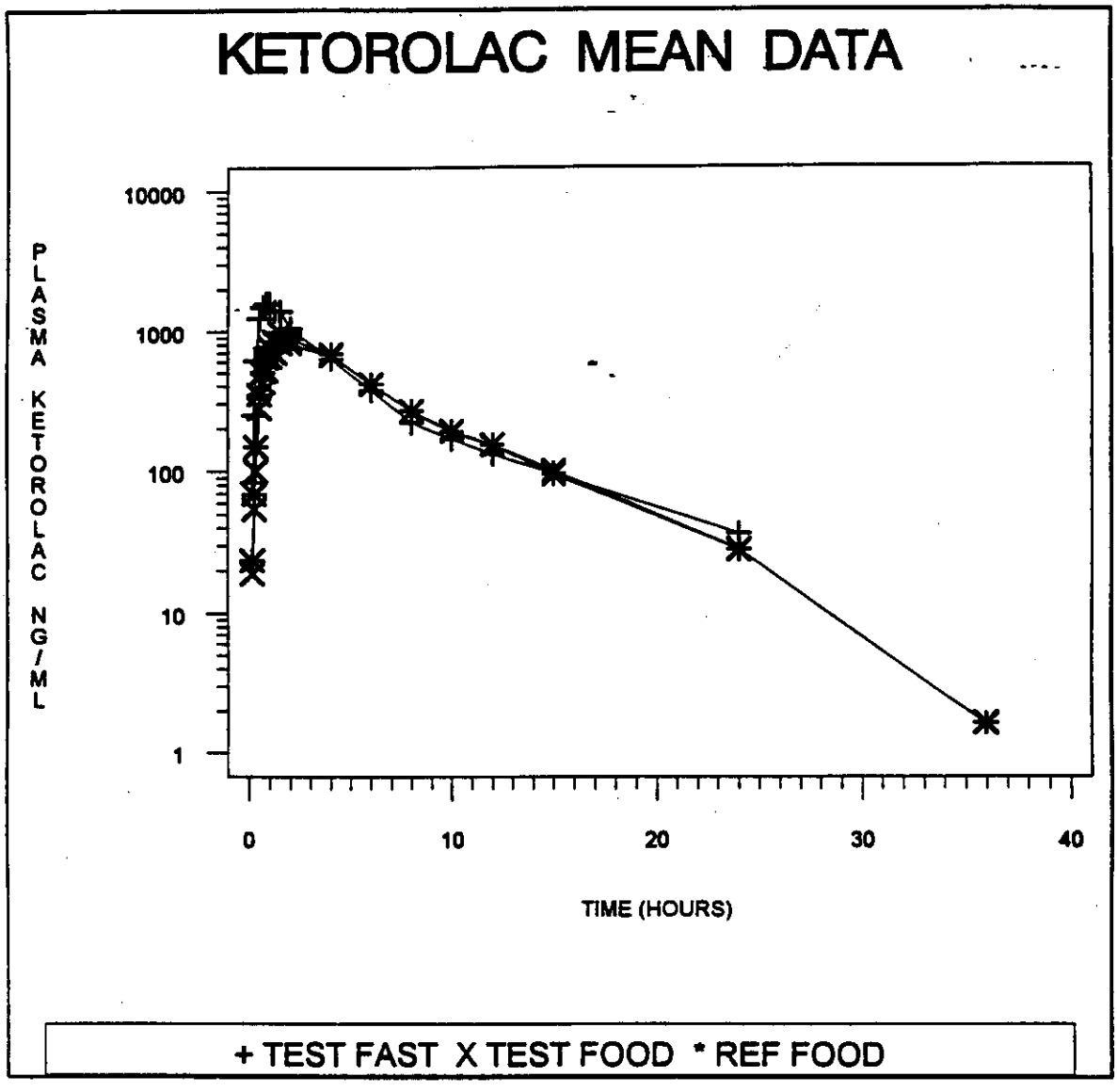
Core Tablet:

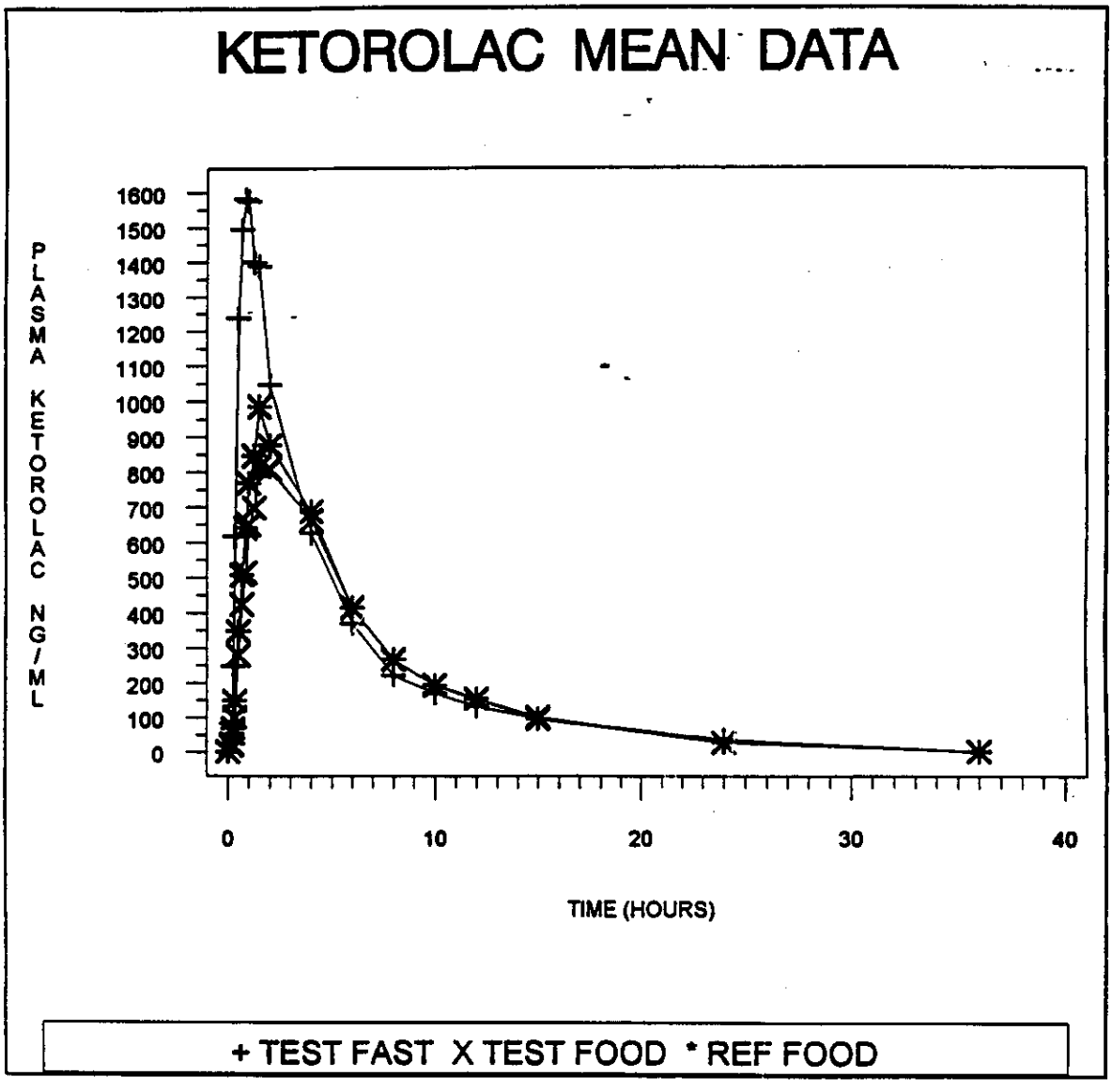
Ingredient	Amount per tablet
Total	**200 mg**

Coating:

VI. In Vitro Dissolution Testing

The conditions and specifications used by the firm are identical to the ones by the USP as described below:


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
10000
1000
100
10
1
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD

1 Analytical Methodology

Since identical assay methodology was used for both fasting and non-fasting studies, no further assay validation data was submitted. No further information is needed on assay validation for this non-fasting study.

2. Pharmacokinetics

According to the Sponsor, of 18 subjects enrolled in the non-fasting study, 15 subjects completed the study. The firm reported the following drop-outs: subject #5 dropped prior to period 3 due to family situation, and 15 dropped prior to period 2 for personal reasons. The total number of subjects completing the study was 16. After the assay, the firm noticed that no valid data can be obtained from subject #9 due to problem with interferences in the chromatograms. Thus total number of subjects whose data were used for bioequivalence determination was 15. The Sponsor indicated that no adverse reactions nor protocol violations were observed in this non-fasting study, except some early or late blood draw times.

Mean plasma concentration-time profiles of all 15 subjects under fasting (test) and non-fasting (test and reference) conditions are shown below:

	Mean Plasma concentration, ng/ml		
Time (Hrs)	Test (%CV, N=15) (Fasting)	Test (%CV, N=15) (Fed)	Ref (%CV, N=15) (Fed)
0.	0.0	0.0	0.0
0.17	83.85 (76.51%)	19.01 (124.55%)	23.6 (82.24%)
0.25	248.25 (55.41%)	54.48 (85.45%)	68.93 (74.92%)
0.33	615.67 (79.90%)	100.59 (81.29%)	148.59 (97.93%)
0.50	1236.93 (51.83%)	279.93 (86.72%)	347.37 (81.54%)
0.67	1493.4 (27.91%)	423.86 (79.71%)	506.7 (71.61%)
0.83	1581.67 (31.04%)	512.84 (66.83%)	640.01 (72.96%)
1.	1575.87 (23.26%)	649.55 (62.29%)	768.60 (60.42%)
1.25	1399.47 (22.61%)	697.33 (50.98%)	845.80 (50.47%)
1.5	1388.0 (26.70%)	816.73 (55.45%)	985.13 (37.10%)
2	1046.6 (20.49%)	809.4 (33.32%)	876.07 (29.47%)
4	624.0 (25.38%)	661.73 (31.07%)	685.93 (29.40%)
6	369.0 (29.43%)	412.2 (36.18%)	413.53 (39.95%)
8	221.0 (24.49%)	265.09 (41.2%)	265.87 (39.65%)
10	169.66 (27.44%)	193.26 (43.54%)	191.31 (41.03%)
12	132.13 (27.62%)	153.62 (51.97%)	154.29 (45.00%)
15	95.43 (46.51%)	100.69 (53.30%)	94.56 (41.17%)
24	36.01 (61.39%)	27.93 (80.22%)	27.79 (72.28%)
36	0.0	1.65 (387.30%)	1.627 (387.30%)

IV. Review of the non-fasting study: Protocol # B-01095.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This will be a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects.

Principal Investigator:

Clinical Study Site:
Company, with . Clinic Director.

Analytical Site: Analytical
Director.

Dose: Two (2) tablets with 240 ml of water. The lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study as follows:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL® (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

Number of subjects: Eighteen males (18), with NO ALTERNATES The same subject selection criteria was used for the fasting and non-fasting studies.

Washout was one week between treatments.

Meal and food restriction:

Fed phase: Subjects will fast for at least 10 hours prior to serving the standard breakfast. Subjects will be instructed to eat the entire breakfast in 30 minutes and the drug will be given 35 minutes after the subjects begin the breakfast. Breakfast composition is as follows: 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 180 ml of orange juice and 240 ml of whole milk.

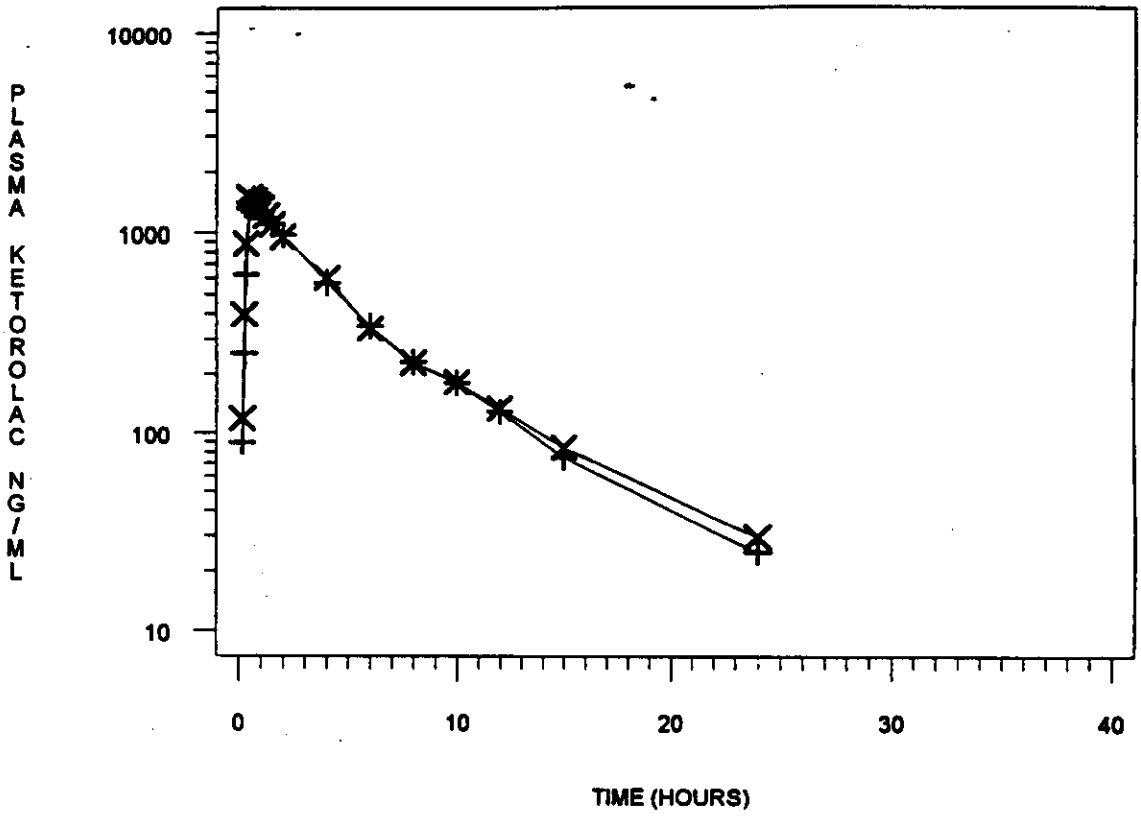
Fasting phase: Subjects will fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, are identical to the fasting study (Protocol # B-01085).

RESULTS

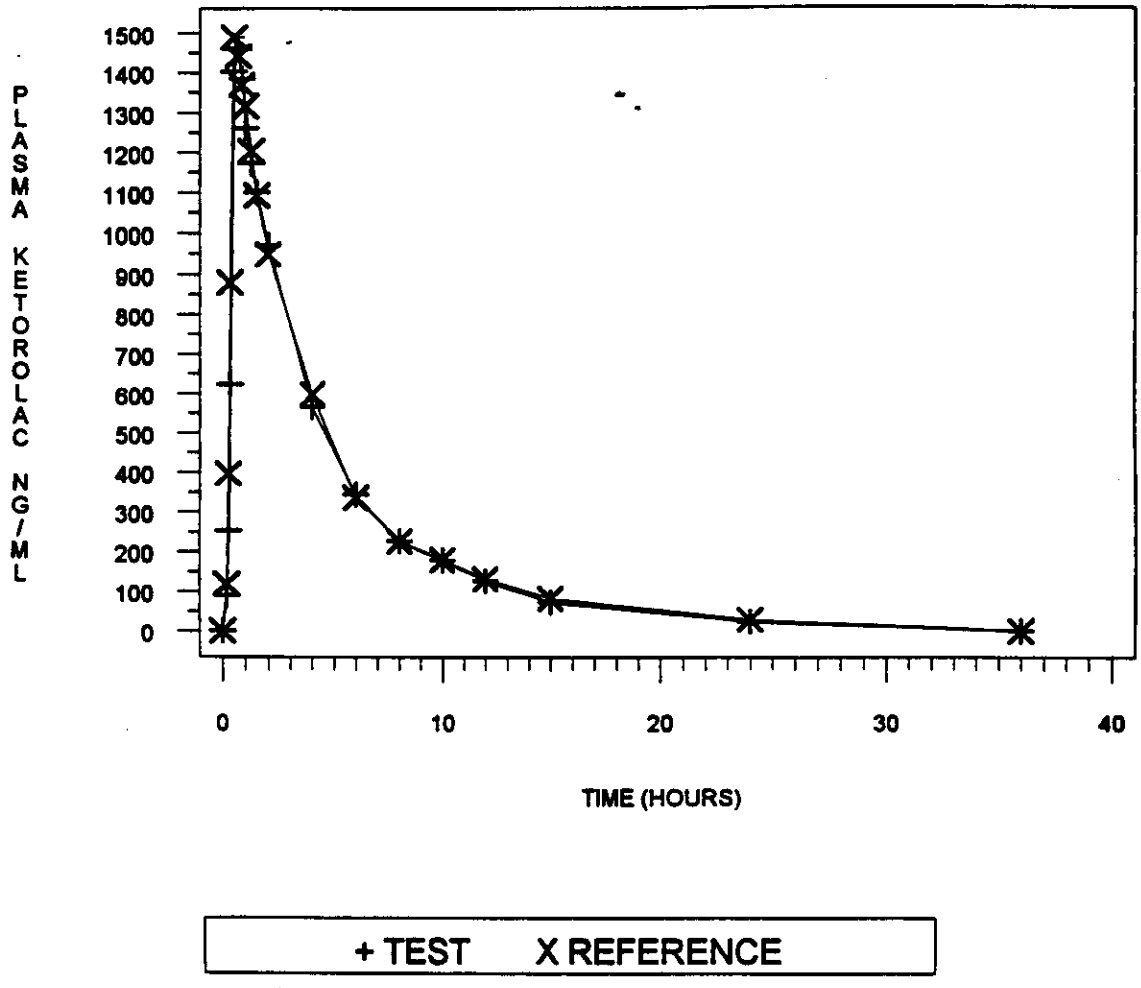
SEMI-LOG PLOT OF

KETOROLAC MEAN DATA



LINEAR PLOT OF

KETOROLAC MEAN DATA



+ TEST X REFERENCE

2. Pharmacokinetics

According to the Sponsor, all 26 subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in only three subjects (subj # 3, 10 and 24) and all were on reference formulation. No therapy was required. The Sponsor also indicated that no significant deviation from the study protocol, except some late blood draw. Mean plasma concentration-time profiles of all 26 subjects under test and reference treatments are shown below:

Mean Plasma concentration, ng/ml

Time (hr)	Test (%CV, N=26)	Ref (%CV, N=26)
0.	0.0	0.0
0.17	89.2 (143.6%)	118.1 (147.5%)
0.25	253.1 (108.2%)	396.1 (122.2%)
0.33	622.8 (83.4%)	878.4 (77.3%)
0.50	1402.6 (48.3%)	1489.1 (43.1%)
0.67	1460.2 (41.7%)	1441.3 (27.5%)
0.83	1383.3 (37.3%)	1368.6 (24.7%)
1.	1262.0 (37.1%)	1314.8 (24.4%)
1.25	1171.9 (28.3%)	1202.9 (24.8%)
1.5	1099.7 (26.2%)	1091.9 (22.1%)
2	969.1 (15.9%)	947.9 (22.5%)
4	565.0 (26.1%)	596.4 (31.5%)
6	343.2 (28.1%)	334.9 (30.4%)
8	226.3 (37.3%)	225.0 (30.4%)
10	177.6 (33.5%)	179.9 (48.7%)
12	126.7 (37.3%)	131.8 (47.3%)
15	73.9 (39.1%)	83.3 (45.5%)
24	24.8 (77.0%)	29.5 (60.1%)
36	0.0	0.0

Mean values of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV)	Ref (%CV)
AUC_{0-t}	6423.6 (21.1%)	6655.0 (22.1%)
$AUC_{0-\infty}$	6722.4 (20.9%)	6943.5 (22.2%)
C_{max}	1733.0 (26.6%)	1713.0 (26.7%)
T_{max} (hrs)	0.98 (80.3%)	0.904 (84.9%)
$T_{1/2}$ (hrs)	5.168 (23.3%)	5.67 (17.6%).

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. 90% confident interval limits were estimated using two one-sided test procedure. Results indicated that, for log transformed and untransformed parameters, all parameters are within the current acceptable limits: AUCt (92.3% - 102%), AUCinf (92.9% - 102%) and Cmax (90.6% - 112%).

Inter-day (N = 3 days)

	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
	98.6%	2.0%	101.0%	2.0%	102.0%	2.1%
Replicate (N)	15	15	15	15	15	15

e. Recovery: Recovery as defined as ratio of QC extracted from plasma/QC unextracted in water was (N = 3) 83.2%, 91.4% and 89.1% for high, medium and low QC respectively. Recovery of the internal standard was 90.6% with N = 3.

f. Freeze-Thaw Stability: Freeze-thaw (F/T), in-process and long term stability studies were done on three QC samples. In-process stability was conducted after 48 hours at room temperature, and long term study was done after 87 days in frozen storage conditions. Results are shown in table below:

	Percent change (N = 3)		
	50 ng/ml	**350 ng/ml**	**2500 ng/ml**
First F/T cycle	-2.6%	2.6%	6.6%
Second F/T cycle	-1.2%	2.3%	7.8%
Third F/T cycle	-1.4%	2.6%	7.9%
In-process	1.8%	-0.3%	4.5%
Long term	-10.8%	5.1%	-0.3%

B. During-Study Validation:

The study had 26 subjects with two periods and 19 sampling points (988 samples). The study samples were assayed in 15 runs. Results of the during study validation reaffirmed the prestudy validation data about linearity of the assay (R = 0.999 or better from 15 runs), specificity (no interference at retention times of drug and internal standard peaks from study subject samples at 0 hour), precision and accuracy as shown below:

Inter-day (N = 15)

	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
	99.0%	2.3%	102.0%	2.0%	100.0%	1.2%
Replicate (N)	30	30	30	30	30	30

Sampling schedule: 10 ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20°C until assay.

Assay Methodology: A specific analytical method ur ketorolac tromethamine in plasma was used. According to a analytical procedure, aliquots of plasma were mixed with a solution of internal standard (tolmetin sodium) and HCl and samples were extracted with an organic solvent. The organic solvent was evaporated to dryness and the residue was reconstituted in mobile phase and inject onto an ;ystem with a

Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

RESULTS

1 Analytical Methodology

Preparation of Standards and Quality Control Samples:
Standards and quality control samples (QC) were prepared in human plasma. Concentrations of standards and QC samples were as follows:

Standards: 20, 50, 100, 200, 500, 1000, 2000, and 3000 ng/ml
QC: **low** (50 ng/ml), **medium** (350 ng/ml) and **high** (2500 ng/ml).

A. Assay Pre-Study Validation:

a. Specificity: Chromatograms submitted by the firm indicated the specificity of the assay. No extra (interference) peaks were seen at the retention times of the drug and internal standard peaks.

b. Sensitivity: The lower limit of detection is 20 ng/ml. At this concentration, for three different days, intra-day accuracy was between 3% to 6.3% (N=3) and precision was between 99.5% to 104% (N=3). Also, at this concentration, inter-day precision and accuracy were 4.4% and 101% respectively, with N=9.

c. Linearity: Using weigting factor of 1/PHR, the standard curves were linear over the 20 ng/ml to 3000 ng/ml range. The correlation coefficient of all runs (N=15 runs) was at least 0.99 or better.

d. Accuracy and Precision:

Intra-day

	QC Sample Concentration					
	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
Day 1	99.0%	1.2%	101.0%	0.2%	100.0%	2.5%
Day 2	97.2%	2.8%	102.2%	2.7%	101.2%	1.5%
Day 3	99.6%	1.3%	98.9%	0.6%	103.2%	0.9%
Replicate (N)	5	5	5	5	5	5

SUMMARY OF THE RESULTS OF THE IN-VIVO BIOEQUIVALENCE STUDIES AND DISSOLUTION TESTING DATA

I. Product Information

The lots of test and reference products used in the comparative studies are:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL® (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

II. Review of the fasting study: Protocol # B-01085.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions.

Principal Investigator: Irwin . Principal Investigator

Clinical Study Site:
Company, with as Clinic Director.
Analytical Site: : Analytical Director.

Dose: Two (2) tablets with 240 ml of water.
Number of subjects: Twenty six males (26), with NO ALTERNATES
Subject selection:
Inclusion Criteria: All males, 18 - 45 years of age, no more than ± 15% from ideal BW, with no history of cardiac, GI diseases and no alcohol or drug abuse as shown by a medical and physical exams were included in the study. Subjects should have no prescription drugs within 14 days, no alcohol consumption for at least 24 hours prior to drug administration, and no known allergy to ketorolac.

Exclusion criteria: Alcoholics, subjects with GI, renal, hepatic diseases, abnormal laboratory measurements, etc. No OTC medications nor alcohol, xanthine containing beverages were allowed during the study.
Approved IRB as well as informed consent were obtained from each subject prior to entry into the study.

Subjects were housed in the acility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.

Nhan L. Tran, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED BY SNerurkar, Ph.D.
FT INITIALED BY SNerurkar, Ph.D.

9/27/1996

Concur:

Date: 9/27/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

was -4.4, -4.9 and -5.4 for high (2500 ng/ml), medium (350 ng/ml) and low (50 ng/ml) concentrations respectively. Under light protected conditions, for 24 hours at room temperature before extraction, the percent change was comparable to the one under normal conditions, i.e., -3.5, -4.3, and -5 for high, medium and low concentrations. The stability of ketorolac in the detector flow cell was demonstrated after 5 and 10 minutes exposure.
The response is acceptable.

Deficiency 4: Complete data with all calculations should be shown to substantiate the choice of using 1/Response as weighting factor vs. other weighting schemes, such as $1/(Response)^2$ or no weight in the regression of the standard curves.

Firm's response: Based on the data submitted using different weighting factors such as 1/C, $1/C^2$ and unweighted linear regression, the contract laboratory (Bioassay) uses 1/C as the weighting factor for the regression of the standard curves.
The response is acceptable.

Deficiency 5: Product Information: Since no expiry date, nor information on theoretical and actual yield were provided for the test formulation, the firm is requested to submit those information for review.

Firm's response: Theoretical yield was tablets and actual yield was tablets. Ratio of actual/theoretical was 78.6 %. The response is acceptable.

IV. .RECOMMENDATIONS

1. The fasted and nonfasted bioequivalence studies conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablet, Lot # 293-117, comparing it to Syntex's TORADOL® 10 mg tablet, Lot # 2541, has been found acceptable to the Division of Bioequivalence. The studies demonstrate that Lemmon's ketorolac tromethamine 10 mg tablets are bioequivalent to the reference product,.Syntex's TORADOL® 10 mg tablets.

2. The dissolution testing conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablet, Lot # 293-117, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 ml of water at 37°C using USP XXIII Apparatus II (Paddle) at 50 rpm. The test product should meet the USP specifications:

From the bioequivalence point of view, the firm has met the ***in-vivo*** bioequivalence and ***in-vitro*** dissolution requirements and the application for Lemmon's ketorolac tromethamine 10 mg tablets, ANDA 74-754 is acceptable.

III. REVIEW OF THE RESPONSES

Deficiency 1: For the fasting and fed studies, the estimation of Kel (hence AUCinf) is not reliable for the following subjects: For fasting study: subject 8 and 9 (test formulation) and subject 10 and 11 (reference formulation), and for the fed study: subject 4 and 6 (test formulation, fasting leg) and subject 2 and 6 (test formulation, fed leg) due to the irregularity of the terminal data points. Hence, it is suggested the firm should submit the following information for consideration:
a. Use appropriate pharmacokinetic model to fit the data of the above subjects, then estimate Kel and AUCinf. Re-do ANOVA and appropriate statistical testings.
b. Delete those subjects in the fasting and fed studies and redo statistical analysis of AUCinf for both studies.
Results of a) and b) should be submitted for comparative evaluation.

Firm's response: The statistical analysis of AUCinf was re-run without the subjects with irregularities of the terminal data points. The 90% C.I. limits (log transformed) on AUCinf for the fasting study were 92.3% - 103%, while the ratio of the geometric means of the AUCinf for the fed study was 97.6%.
The firm's response is acceptable.

Deficiency 2: For the fed study, detail information on chromatographic interference on subject 9 should be provided. All chromatograms for this subject should be submitted for evaluation.

Firm's response: The pre-dose chromatograms from all three periods for subject #9 have a peak eluting at about 5.4 minutes retention time. This peak co-elutes with ketorolac peak at 5.1 minutes retention time. Due to this interference, accurate quantitation is not possible.
FDA's Comment: From the chromatograms submitted, it is observed that the following samples were affected: For the test (fed leg): sample #400, (0hr),445 (12hrs), 454 (36 hrs), for the reference (fed leg): sample # 401 (0hr), 404 (0.17hr), 407 (0.25hr), 410 (0.33hr), 413 (0.5hr), 416 (0.67hr), 419 (0.83hr), 422 (1hr), 452 (24 hrs) and 455 (36hrs), for the test (fasted leg): sample # 402 (0hr), 405 (0.17hr), 450 (12hrs), 451 (15hrs), 453 (24hrs) and 456 (36hrs). The most affected leg was the reference (fed leg), since more than 50% of the samples cannot be used (10 out of 19 samples were contaminated). Therefore, we concur with the Sponsor that this subject should not be used for bioequivalent determination.
The response is acceptable.

Deficiency 3: Data on photodecomposition of ketorolac should be provided. Comparative data on the extent of the stability of the samples under normal conditions and light-protected conditions should be provided. The extent of the photodecomposition of the samples by UV light . ') during the run should be provided.

Firm's response: The firm provided stability information as follows: For 24 hours at room temperature before extraction under normal conditions, the percent change

The subjects were housed in the acility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.
A ten (10) ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20°C until assay.
A specific analytical method r ketorolac tromethamine in plasma was used. According to a nalytical procedure, aliquots of plasma were mixed with a solution of internal standard (tolmetin sodium) and HCl and samples were extracted with an organic solvent. The organic solvent was evaporated to dryness and the residue was reconstituted in mobile phase and inject onto an system with a
Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

Non-fasting study: Protocol # B-01095.

The objective was to compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This was a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects. The procedures, sites of clinical and analytical studies for this study, etc. were identical to the fasting study. The dose: Two (2) tablets, and the lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study. Washout was one week between treatments.
Meal and food restriction:

Fed phase: Subjects were fasted for at least 10 hours prior to serving the standard breakfast. Subjects were instructed to eat the entire breakfast in 30 minutes and the drug was given 35 minutes after the subjects began the breakfast. Breakfast composition was as follows:

1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk.

Fasting phase: Subjects were fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, were identical to the fasting study (Protocol # B-01085).

SEP 27 1996

Ketorolac Tromethamine
10 mg tablet
Reviewer: Nhan L. Tran
ANDA 74-754
74754SD.596

Lemmon Pharmaceuticals
Sellersville, PA
Submission date:
May 14, 1996.

REVIEW OF A SUPPLEMENT

I. BACKGROUND

Ketorolac tromethamine is a chiral (R and S forms) non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Only the S form is reported to have analgesic activity. Ketorolac tromethamine is more than 99% protein bound, mostly bound to albumin.
When given orally, the bioavailability is at least 80% and the drug does not undergo first pass metabolism. Mean plasma Cmax is about 0.87 mcg/ml after single dose of 10 mg, with a Tmax of about 40 minutes. Plasma terminal half-life is about 5 to 6 hrs for the racemate. Ketorolac is mostly metabolized in the liver, and metabolic products are largely hydroxylated and conjugated forms of the parent drug.
Oral administration of ketorolac after a high fat meal results in lowering Cmax and prolonging Tmax by about 1 hour. The extent of absorption measured by AUC, and the half-life (T1/2) are not affected.
The drug is presently marketed by Syntex under the trade name TORADOL®, 10 mg tablets, and also is available in injectable dosage forms (15 mg, 30 mg and 60 mg for IM injection and 15 mg and 30 mg for IV Bolus injection).

The Sponsor submitted two biostudies (fasting and fed) on September 21, 1995. The studies were reviewed by the Agency on March 6, 1996 and it was found that the studies were deficient. In this supplement, the firm is responding to the deficiencies cited by the Agency in the review of March 1996.

II. SUMMARY OF THE STUDIES

Fasting study: Protocol # B-01085.

The objective of the study was to compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL® 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions. The study was conducted at or Lemmon Company, with as Clinic Director. The analytical site was L with as Analytical Director. The dose was two (2) tablets and the number of subjects was 26 males with NO ALTERNATES.

cc:

Letter Out, Bio Acceptable

Endorsements: /

DRAFTED: STM 09/30/96 X:\WPFILE\BIO\FINAL\N74754.APP

MAR 6 1996

Ketorolac Tromethamine
10 mg tablet
Reviewer: Nhan L. Tran
ANDA 74-754

Lemmon Pharmaceuticals
Sellersville, PA
Submission date:
September 21, 1995.

Review Of Two Bioequivalence Studies (Fasting and Fed) and A Dissolution Data.

I. Background

General Note **NOT FOR FOI:**
"This application by Lemmon is one of the applications we have in house at the present time (March 1, 96) for this drug product. Of all applications whose BIO studies have been reviewed by the Division of Bioequivalence (Novopharm 74-581, Hamilton 74-427, Mylan 74-761 and Lemmon 74-754), only Mylan had acceptable fasting and fed studies. However, Mylan's application is not yet approved by the Agency (OGD) as of to date (3/4/96)".

Ketorolac tromethamine is a chiral (R and S forms) non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, antipyretic and analgesic activities. Only the S form is reported to have analgesic activity. Ketorolac tromethamine is more than 99% protein bound, mostly bound to albumin.
When given orally, the bioavailability is at least 80% and the drug does not undergo first pass metabolism. Mean plasma Cmax is about 0.87 mcg/ml after single dose of 10 mg, with a Tmax of about 40 minutes. Plasma terminal half-life is about 5 to 6 hours for the racemate. Ketorolac is mostly metabolized in the liver, and the metabolic products are largely hydroxylated and conjugated forms of the parent drug.

Oral administration of ketorolac after a high fat meal results in lowering Cmax and prolonging Tmax by about 1 hour. The extent of absorption measured by AUC, and the half-life (T1/2) are not affected.
The drug is presently marketed by Syntex under the trade name TORADOL^{R}, 10 mg tablets, and also is available in injectable dosage forms (15 mg, 30 mg and 60 mg for IM injection and 15 mg and 30 for IV Bolus injection).

II. Product Information

The lots of test and reference products used in the comparative studies are:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL^{R} (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

III. Review of the fasting study: Protocol # B-01085.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL[R] 10 mg tablets by Syntex, in healthy male volunteers under fasting conditions.

Principal Investigator: , Principal Investigator

Clinical Study Site: for Lemmon Company, with as Clinic Director.

Analytical Site: ikhari: Analytical Director.

Dose: Two (2) tablets with 240 ml of water.

Number of subjects: Twenty six males (26), with NO ALTERNATES

Subject selection:

Inclusion Criteria: All males, 18 - 45 years of age, no more than ± 15% from ideal BW, with no history of cardiac, GI diseases and no alcohol or drug abuse as shown by a medical and physical exams were included in the study. Subjects should have no prescription drugs within 14 days, no alcohol consumption for at least 24 hours prior to drug administration, and no known allergy to ketorolac.

Exclusion criteria: included subjects with GI, renal, hepatic diseases, alcoholics, abnormal laboratory measurements, etc. No OTC medications nor alcohol, xanthine containing beverages were allowed during the study. Approved IRB as well as informed consent were obtained from each subject prior to entry into the study.

Subjects were housed in the Gateway facility from at least 12 hours prior to and at least 24 hours after the drug administration. Subjects were not permitted to smoke from one hour prior to and until 4 hours after the drug administration. Washout period was at least one (1) week between dose. Subjects were fasted for at least 10 hours prior to and 5 hours after the drug administration. Water was given ad lib except within 1 hour of drug administration.

Sampling schedule: 10 ml blood sample was collected at pre-dose, and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 15, 24, and 36 hours. Plasma was separated and frozen at -20^{0}C until assay.

Assay Methodology: A specific analytical method or ketorolac tromethamine in plasma was used. According to a ' ry analytical procedure, aliquots of plasma were mixed with a solution of internal standard and HCl and samples were extracted with an organic solvent. The organic solvent was evaporated to dryness and the residue was reconstituted in mobile phase and inject onto an ystem equipped with a '

Pharmacokinetic and statistical analyses: AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were calculated. ANOVA and 90% C.I. limits (two-one sided test) were used for all important pharmacokinetic parameters.

RESULTS

1 Analytical Methodology

Preparation of Standards and Quality Control Samples:
Standards and quality control samples (QC) were prepared in human plasma. Concentrations of standards and QC samples were as follows:

Standards: 20, 50, 100, 200, 500, 1000, 2000, and 3000 ng/ml
QC: **low** (50 ng/ml), **medium** (350 ng/ml) and **high** (2500 ng/ml).

A. Assay Validation:

A1. Pre-Study Validation:

a. Specificity: Chromatograms submitted by the firm indicated the specificity of the assay. No extra (interference) peaks were seen at the retention times of the drug and internal standard peaks.

b. Sensitivity: The lower limit of detection is 20 ng/ml. At this concentration, for three different days, intra-day accuracy was between 3% to 6.3% (N=3) and precision was between 99.5% to 104% (N=3). Also, at this concentration, inter-day precision and accuracy were 4.4% and 101% respectively, with N=9.

c. Linearity: Using weigting factor of 1/PHR, the standard curves were linear over the 20 ng/ml to 3000 ng/ml range. The correlation coefficient of all runs (N = 15 runs) was at least 0.99 or better.

d. Accuracy and Precision:

Intra-day

	QC Sample Concentration					
	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
Day 1	99.0%	1.2%	101.0%	0.2%	100.0%	2.5%
Day 2	97.2%	2.8%	102.2%	2.7%	101.2%	1.5%
Day 3	99.6%	1.3%	98.9%	0.6%	103.2%	0.9%
Replicate (N)	5	5	5	5	5	5

Inter-day (N=3)

	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
	98.6%	2.0%	101.0%	2.0%	102.0%	2.1%
Replicate (N)	15	15	15	15	15	15

e. **Recovery:** Recovery as defined as ratio of QC extracted from plasma/QC unextracted in water was (N=3) 83.2%, 91.4% and 89.1% for high, medium and low QC respectively. Recovery of the internal standard was 90.6% with N=3.

f. **Freeze-Thaw Stability:** Freeze-thaw (F/T), in-process and long term stability studies were done on three QC samples. In-process stability was conducted after 48 hours at room temperature, and long term study was done after 87 days in frozen storage conditions. Results are shown in table below:

	Percent change (N=3)		
	50 ng/ml	350 ng/ml	2500 ng/ml
First F/T cycle	-2.6%	2.6%	6.6%
Second F/T cycle	-1.2%	2.3%	7.8%
Third F/T cycle	-1.4%	2.6%	7.9%
In-process	1.8%	-0.3%	4.5%
Long term	-10.8%	5.1%	-0.3%

A2. During-Study Validation:

The study had 26 subjects with two periods and 19 sampling points (988 samples). The study samples were assayed in 15 runs. Results of the during study validation reaffirmed the prestudy validation data about linearity of the assay (R = 0.999 or better from 15 runs), specificity (no interference at retention times of drug and internal standard peaks from study subject samples at 0 hour), precision and accuracy as shown below:

Inter-day (N=15)

	50 ng/ml		350 ng/ml		2500 ng/ml	
	Accuracy	Precision	Accuracy	Precision	Accuracy	Prec.
	99.0%	2.3%	102.0%	2.0%	100.0%	1.2%
Replicate (N)	30	30	30	30	30	30

2. Pharmacokinetics

According to the Sponsor, all 26 subjects completed the study. Minor adverse reactions such as emesis, diarrhea and light headache occurred in only three subjects (subj # 3, 10 and 24) and all were on reference formulation. No therapy was required. The Sponsor also indicated that no significant deviation from the study protocol, except some late blood draw. Mean plasma concentration-time profiles of all 26 subjects under test and reference treatments are shown below:

Mean Plasma concentration, ng/ml

Time (hr)	Test (%CV, N=26)	Ref (%CV, N=26)
0.	0.0	0.0
0.17	89.2 (143.6%)	118.1 (147.5%)
0.25	253.1 (108.2%)	396.1 (122.2%)
0.33	622.8 (83.4%)	878.4 (77.3%)
0.50	1402.6 (48.3%)	1489.1 (43.1%)
0.67	1460.2 (41.7%)	1441.3 (27.5%)
0.83	1383.3 (37.3%)	1368.6 (24.7%)
1.	1262.0 (37.1%)	1314.8 (24.4%)
1.25	1171.9 (28.3%)	1202.9 (24.8%)
1.5	1099.7 (26.2%)	1091.9 (22.1%)
2	969.1 (15.9%)	947.9 (22.5%)
4	565.0 (26.1%)	596.4 (31.5%)
6	343.2 (28.1%)	334.9 (30.4%)
8	226.3 (37.3%)	225.0 (30.4%)
10	177.6 (33.5%)	179.9 (48.7%)
12	126.7 (37.3%)	131.8 (47.3%)
15	73.9 (39.1%)	83.3 (45.5%)
24	24.8 (77.0%)	29.5 (60.1%)
36	0.0	0.0

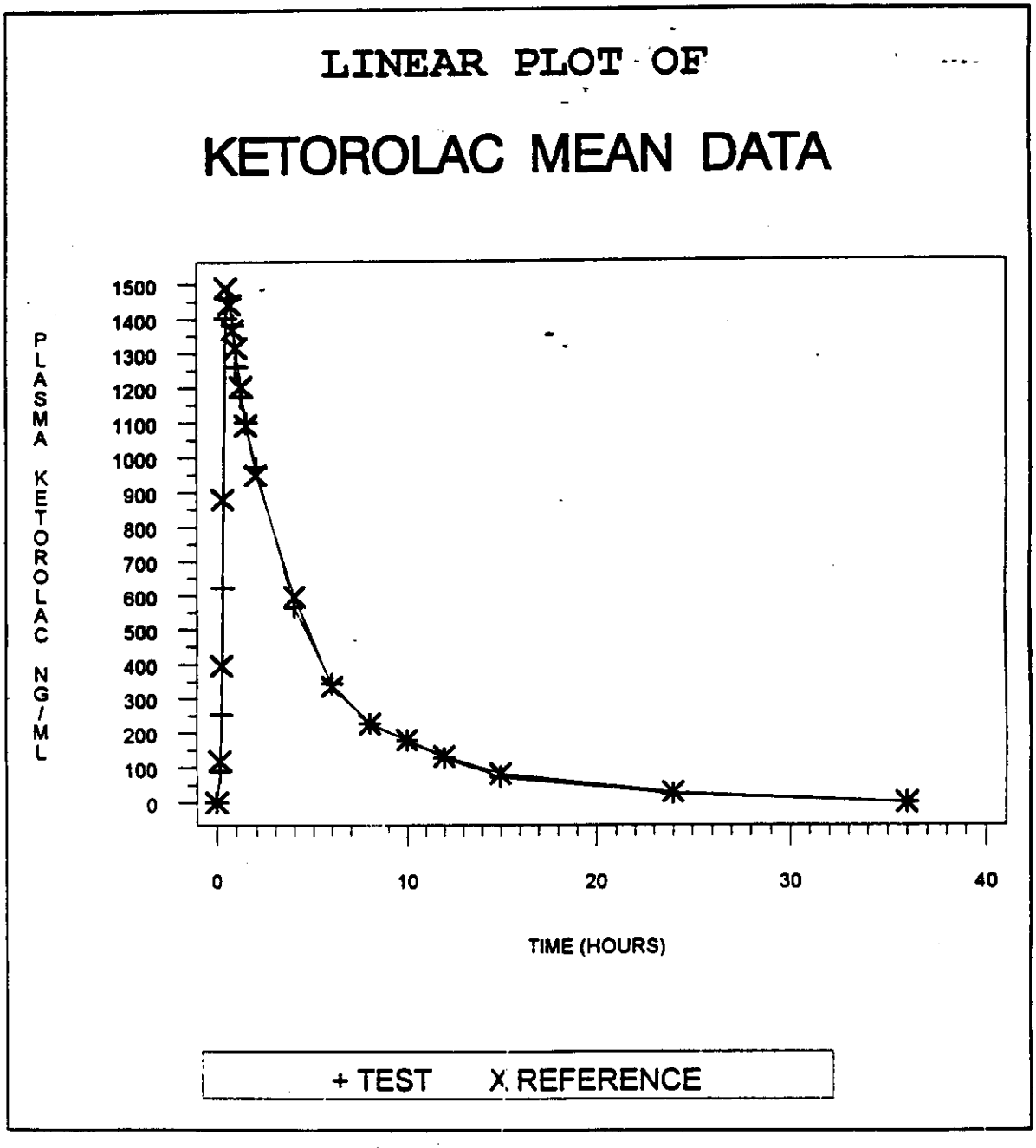
Mean values of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV)	Ref (%CV)
AUC_{0-t}	6423.6 (21.1%)	6655.0 (22.1%)
$AUC_{0-\infty}$	6722.4 (20.9%)	6943.5 (22.2%)
C_{max}	1733.0 (26.6%)	1713.0 (26.7%)

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. 90% confident interval limits were estimated using two one-sided test procedure. Results indicated that, for log transformed and untransformed parameters, all parameters are within the current acceptable limits: AUCt (92.3% - 102%), AUCinf (92.9% - 102%) and Cmax (90.6% - 112%).

IV. Review of the non-fasting study: Protocol # B-01095.

Objective: To compare the bioavailability of a generic ketorolac tromethamine 10 mg tablets (Lemmon Company) with that of TORADOL^{R} 10 mg tablets by Syntex, in healthy male volunteers under fasting and fed conditions.
This will be a single dose, randomized, 3-way cross-over (test: fed and fasting, and reference: fed) in 18 subjects.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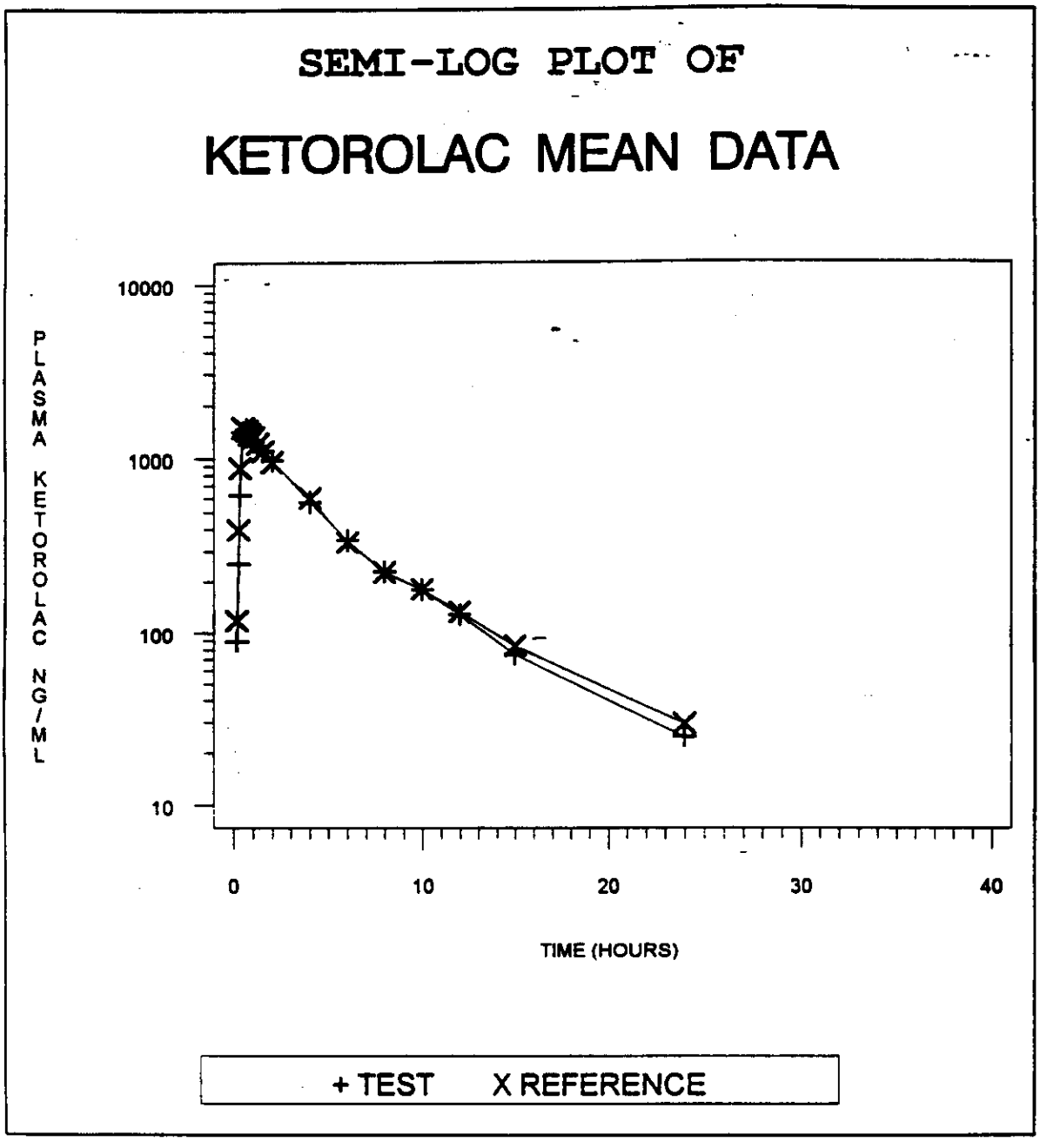
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TIME (HOURS)
+ TEST X REFERENCE

Principal Investigator: Principal Investigator

Clinical Study Site: non
Company, with Daniel Shipley as Clinic Director.

Analytical Site: Analytical
Director.

Dose: Two (2) tablets with 240 ml of water. The lots of test and reference products used in the comparative studies are identical to the ones used in the fasting study as follows:

Test: LEMMON's ketorolac tromethamine tablets USP, 10 mg, lot # 0293-117, lot (batch) size: No expiry date, nor information on theoretical and actual yield were provided. Content uniformity: 99.2%.

Reference: SYNTEX's TORADOL^{R} (ketorolac tromethamine) 10 mg tablets, lot # 02541, expiry date: 2/96. Content uniformity: 98.7%.

Number of subjects: Eighteen males (18), with NO ALTERNATES The same subject selection criteria was used for the fasting and non-fasting studies.

Washout was one week between treatments.

Meal and food restriction:

Fed phase: Subjects will fast for at least 10 hours prior to serving the standard breakfast. Subjects will be instructed to eat the entire breakfast in 30 minutes and the drug will be given 35 minutes after the subjects begin the breakfast. Breakfast composition is as follows:

1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving of hash brown potatoes
180 ml of orange juice
240 ml of whole milk.

Fasting phase: Subjects will fast for at least 10 hours prior to and 5 hours after drug administration.

Other procedures such as analytical, sampling schedule, are identical to the fasting study (Protocol # B-01085).

RESULTS

1 Analytical Methodology

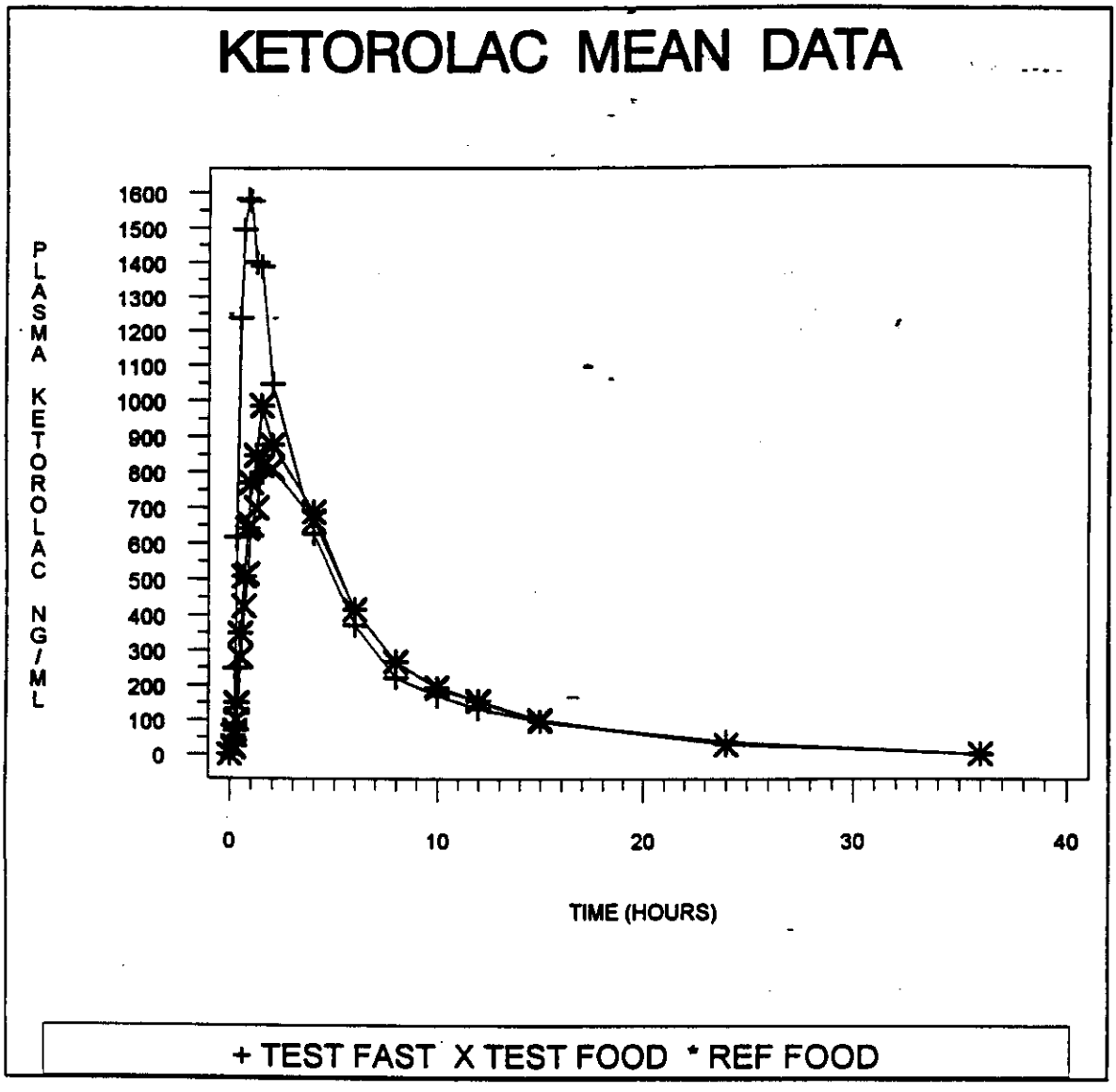
Since identical assay methodology was used for both fasting and non-fasting studies, no further assay validation data was submitted. No further information is needed on assay validation for this non-fasting study.

2. Pharmacokinetics

According to the Sponsor, of 18 subjects enrolled in the non-fasting study, 15 subjects completed the study. The firm reported the following drop-outs: subject #5 dropped prior to period 3 due to family situation, and 15 dropped prior to period 2 for personal reasons. The total number of subjects completing the study was 16. After the assay, the firm noticed that no valid data can be obtained from subject #9 due to problem with interferences in the chromatograms. Thus total number of subjects whose data were used for bioequivalence determination was 15. The Sponsor indicated that no adverse reactions nor protocol violations were observed in this non-fasting study, except some early or late blood draw times.

Mean plasma concentration-time profiles of all 15 subjects under fasting (test) and non-fasting (test and reference) conditions are shown below:

	Mean Plasma concentration, ng/ml		
Time (Hrs)	Test (%CV, N=15) (Fasting)	Test (%CV, N=15) (Fed)	Ref (%CV, N=15) (Fed)
0.	0.0	0.0	0.0
0.17	83.85 (76.51%)	19.01 (124.55%)	23.6 (82.24%)
0.25	248.25 (55.41%)	54.48 (85.45%)	68.93 (74.92%)
0.33	615.67 (79.90%)	100.59 (81.29%)	148.59 (97.93%)
0.50	1236.93 (51.83%)	279.93 (86.72%)	347.37 (81.54%)
0.67	1493.4 (27.91%)	423.86 (79.71%)	506.7 (71.61%)
0.83	1581.67 (31.04%)	512.84 (66.83%)	640.01 (72.96%)
1.	1575.87 (23.26%)	649.55 (62.29%)	768.60 (60.42%)
1.25	1399.47 (22.61%)	697.33 (50.98%)	845.80 (50.47%)
1.5	1388.0 (26.70%)	816.73 (55.45%)	985.13 (37.10%)
2	1046.6 (20.49%)	809.4 (33.32%)	876.07 (29.47%)
4	624.0 (25.38%)	661.73 (31.07%)	685.93 (29.40%)
6	369.0 (29.43%)	412.2 (36.18%)	413.53 (39.95%)
8	221.0 (24.49%)	265.09 (41.2%)	265.87 (39.65%)
10	169.66 (27.44%)	193.26 (43.54%)	191.31 (41.03%)
12	132.13 (27.62%)	153.62 (51.97%)	154.29 (45.00%)
15	95.43 (46.51%)	100.69 (53.30%)	94.56 (41.17%)
24	36.01 (61.39%)	27.93 (80.22%)	27.79 (72.28%)
36	0.0	1.65 (387.30%)	1.627 (387.30%)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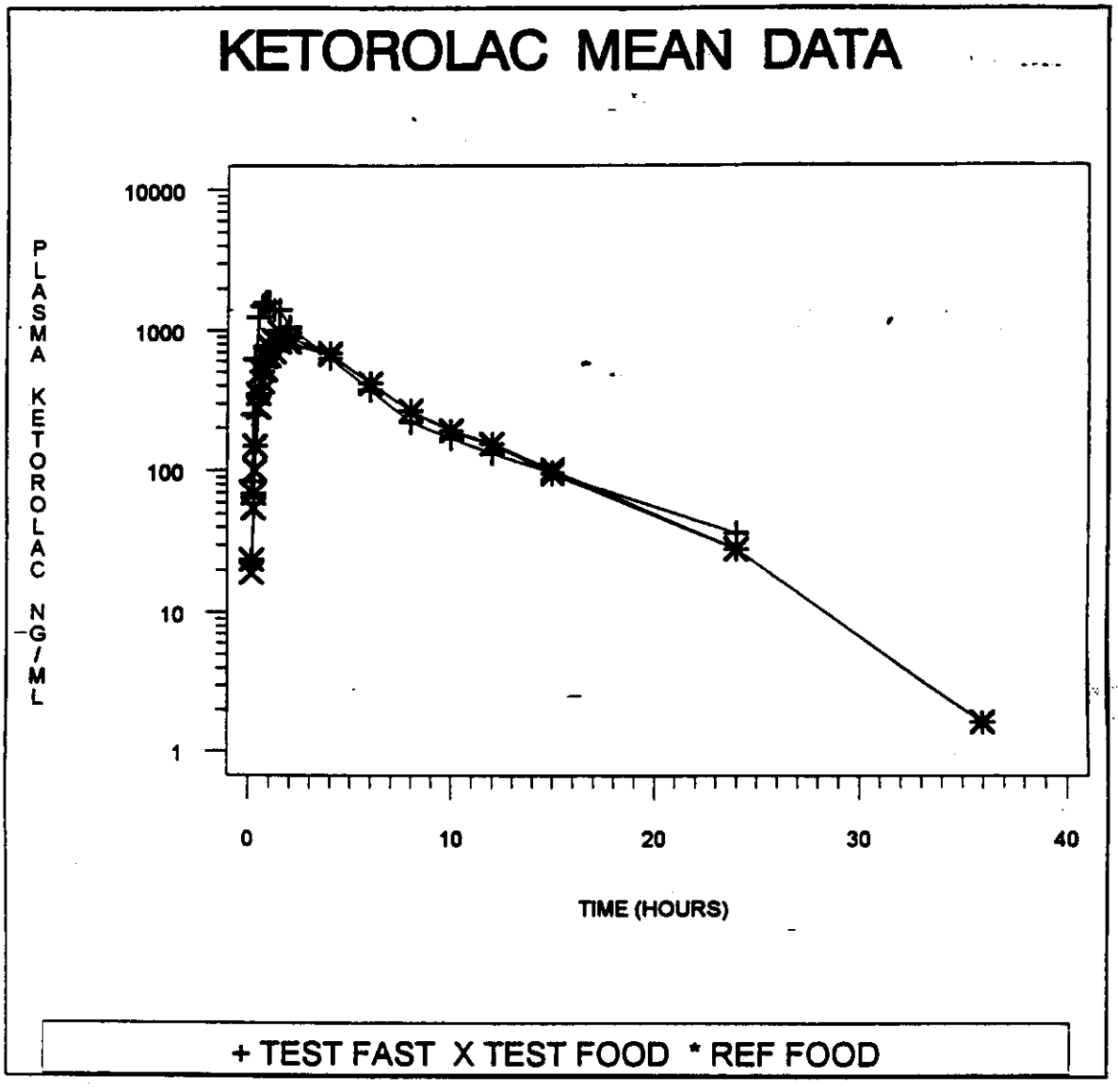
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD


KETOROLAC MEAN DATA
PLASMA KETOROLAC NG/ML
10000
1000
100
10
1
0
10
20
30
40
TIME (HOURS)
+ TEST FAST X TEST FOOD * REF FOOD

Means (N = 15) of important pharmacokinetic parameters are shown below:

Parameter	Test (%CV) (Fast)	Test (%CV) (Fed)	Ref (%CV) (Fed)
AUC_{0-t}	7136.83 (21.88%)	5992.38 (26.05%)	6266.08 (24.37%)
$AUC_{0-\infty}$	7528.05 (22.16%)	6302.95 (25.28%)	6569.65 (23.01%)
C_{max}	1936.60 (21.58%)	1055.20 (24.40%)	1198.47 (25.07%)

ANOVA was performed on all parameters and terms such as sequence, sub(sequence), period and treatment were included in the statistical model. From the ANOVA output, least squares means (log transformed data) of the test and reference formulations were obtained and they were used for the estimation of the ratios of test/reference for AUCt, AUCinf, and Cmax. For the log transformed data, this ratio can be estimated as [$100xe^{(LSMtest-LSMreference)}$], with the least-squares mean (LSM) computed by using the LSMEANS statement in the SAS GLM procedure.

Results indicated that, for log transformed parameters, the ratios of the test and reference formulations under nonfasting conditions for ***AUCt (96.0%), AUCinf (96.2%) and Cmax (90.5%), all are within the current acceptable ratio limits of 80% to 125%.***

V. Composition of the test tablets

Core Tablet:

Ingredient	Amount per tablet
Total	**200 mg**

Coating:

VI. In Vitro Dissolution Testing

The conditions and specifications used by the firm are identical to the ones by the USP as described below:

In Vitro Dissolution Testing

Drug: Ketorolac Tromethamine, Dose Strength: 10 mg, Tablet
ANDA No.: 74-754, Firm: Lemmon
Submission Date: September 21, 1995
File Name: 74754SD.995

I. Conditions for Dissolution Testing:

USP XXII, Paddle: RPM: 50, 600 ml, water, No. Units Tested: 12
Specifications: I
Reference Drug: TORADOL^{R} 10 mg Tablets by SYNTEX.
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (min)	Test Product Lot # 293-117, Strength: 10 mg			Reference Product Lot # 2541, Strength: 10 mg.		
	Mean %	Range	%CV	Mean %	Range	%CV
15	89.6		13.5	93.5		8.2
30	97.3		7.4	98.1		4.9
45	99.0		5.5	100.3		3.6
60	99.7		4.4	101.3		3.0

VII. Deficiencies

1. For the fasting and fed studies, the estimation of Kel (hence AUCinf) is not reliable for the following subjects: For fasting study: subject 8 and 9 (test formulation) and subject 10 and 11 (reference formulation), and for the fed study: subject 4 and 6 (test formulation, fasting leg) and subject 2 and 6 (test formulation, fed leg) due to the irregularity of the terminal data points. Hence, it is suggested the firm should submit the following information for consideration:

a. Use appropriate pharmacokinetic model to fit the data of the above subjects, then estimate Kel and AUCinf. Re-do ANOVA and appropriate statistical testings.

b. Delete those subjects in the fasting and fed studies and redo statistical analysis of AUCinf for both studies.

Results of a) and b) should be submitted for comparative evaluation.

2. For the fed study, detail information on chromatographic interference on subject 9 should be provided. All chromatograms for this subject should be submitted for evaluation.

3. Data on photodecomposition of ketorolac should be provided. Comparative data on the extent of the stability of the samples under normal conditions and light-protected conditions should be provided. The extent of the photodecomposition of the samples by ight during the run should be provided.

4. Complete data with all calculations should be shown to substantiate the choice of using 1/Response as weighting factor vs. other weighting schemes, such as $1/(Response)^2$ or no weight in the regression of the standard curves.

5. Product Information: Since no expiry date, nor information on theoretical and actual yield were provided for the test formulation, the firm is requested to submit those information for review.

VIII. Recommendations

1. The bioequivalence studies conducted by Lemmon Company on its ketorolac tromethamine 10 mg tablets, Lot # 293-117, comparing it to Syntex's TORADOL^R Lot # 2541, 10 mg tablets, has been found incomplete by the Division of Bioequivalence due to Deficiencies 1 - 5 above.

2. The dissolution data submitted by the firm is acknowledged.

Nhan L. Tran, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED BY RPatnaik, Ph.D.
FT INITIALED BY RPatnaik, Ph.D. 3/6/96

Concur: Date: 3/6/96

Keith Chan, Ph.D.
Director, Division of Bioequivalence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

UEST TYPE *(Check One)* Original ☐ FollowUp ☐ FUR	DATE January 24, 1996	PHONE NO. 594-0310	EER ID #
REQUESTORS NAME: John Smith	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-623
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-754			
BRAND NAME: Toradol	ESTABLISHED NAME: Ketorolac Tromethamine Tablets		
DOSAGE STRENGTH: 10 mg			STERILE ☐Yes ☒ No
PROFILE CLASS:: TCM	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Lemmon Company			
APPLICANT'S ADDRESS: 650 Cathill Road Sellersville PA 18960			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY ~	
1. d	Manufacturer of NDS				
		CCS			
2. Lemmon Company 650 Cathill Road Sellersville, PA 18960	Manufacture, processing, packaging labeling, handling of the finished drug product				
3.	Testing lab				
		NEC			
4.	Testing lab				
		NEC			
5.	Testing lab				
		NEC			
6. abs, Inc.	Testing lab				
		NEC			
7. nc.	Testing lab				
		NEC			
8. , Inc.	Testing lab				
		NEC			

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 74-754 HFD-/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-/JSimmons HFD-/GJSmith x:\wpfile\eerforms\74754