CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74879

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-879 SPONSOR: Elan Pharmaceutical
DRUG: Ketoprofen Extended Release
DOSAGE FORM: Capsules
STRENGTH(s): 200 mg
TYPE OF STUDY: Single (Multiple) (Fasting/Fed)
STUDY SITE: Pharmaco International, Inc. Austin, TX

STUDY SUMMARY: Fasting, Non fasting and steady State bioStudies Showed Comparable AUC, Cmax and Tmax. The 90% confidence intervals and Geometric mean ratios were within 0.8 to 1.25. The Cmin and degree of fluctuation were comparable for both products and the Study was acceptable to the Div. of bio

DISSOLUTION: The dissolution was conducted in 900 mL of PO4 buffer pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The specification was 1st Hr NLT %-NMT %; 2nd Hour, NLT %-NMT %; 4th Hour, NLT % & NMT % 6th Hours, NLT %-NMT %; 12 Hour NLT %. The dissolution was acceptable.

PRIMARY REVIEWER: BRANCH:

INITIAL: /S/ DATE: 9/16/96

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 9/16/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 9/30/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: N/A DATE:

THE DISSOLUTION SPECIFICATIONS ARE AMENDED AS PER DR. SATHE'S REVIEW DATED 12/2/1997 (ATTACHED).

/S/ 12/4/97

JUL 24 1997

Ketoprofen Extended Release	**Elan Pharmaceutical**
200 mg Capsules	**Gainesville, Georgia**
ANDA # 74-879	**Submission Date:**
Reviewer: Man M. Kochhar	**November 25, 1996**

Amendment to the Review of Correspondence, ANDA # 74-879

Background:

The firm has requested that the Division of Bioequivalence reconsider the dissolution specifications. The firm is requesting five time points instead of six time points.

Comments:

1. Inadvertently I copied the reference dissolution values under the test column and test dissolution values under the reference column. Therefore, the dissolution specifications were based upon the reference product and not on the test product. The new dissolution specifications are based upon the test product.

2. The previous tentative dissolution specifications required six time points as follows:

	Amount dissolved
1 hour	NLT ___ % and not more than ___ %
2 hours	NLT ___ % and not more than ___ %
4 hours	NLT ___ % and not more than ___ %
6 hours	NLT ___ % and not more than ___ %
10 hours	NLT ___ % and not more than ___ %
24 hours	NLT ___ % ___

3. The tentative dissolution specifications can be reconsidered to have five time points as suggested by the firm. USP XXIII monographs allows five time points for extended release tablets or capsules. The time points should be as follows:

1 hour	NLT ___ % and not more than ___ %
2 hours	NLT ___ % and not more than ___ %
4 hours	NLT ___ % and not more than ___ %
8 hours	NLT ___ % and not more than ___ %
10 hours	NLT ___ % ___

4. The firm should be allowed to conduct dissolution using 5 time points as mentioned in comment # 3.

RECOMMENDATIONS:

1. The fasting, non-fasting, and multiple-dose bioequivalence studies conducted by Elan Labs on its Ketoprofen Extended Release, 200 mg capsules, lot # C5J1932, comparing it to Oruvail capsules, 200 mg, lot # 9950321, manufactured by Wyeth Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules are bioequivalent to the reference product Oruvail 200 mg capsules manufactured by Wyeth Ayerst.

2. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

	Amount Dissolved
1 Hours	not less than % and not more than %
2 Hours	not less than % and not more than %
4 Hours	not less than % and not more than %
8 Hours	not less than % and not more than %
10 Hours	not less than %

The interim specifications are based on the further review of the dissolution data on the bio lot. The final dissolution specifications will be set upon review of the dissolution data on atleast 3 production batches.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing and the study is acceptable.

The firm should be informed of the new recommendations.

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 7/22/97
Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: /S/ Date: 7/24/97
for Nicholas M. Fleischer, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/7-8-97; BIO Addendum

Table 1 . In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen ER
Dose Strength: 200 mg
ANDA No.: 74-879
Firm: Elan Labs
Submission Date: April 1, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 phosphate buffer, pH 7.2

		Sponsor's	Division of Bioequivalence
Specifications:	1 Hour	between %	between % and %
	2 Hours	between %	between % and %
	4 Hours	between %	between % and %
	8 Hours		Between % and %
	10 Hours	between %	NLT 70%
	24 Hours	NLT 85%	

Reference Drug: Oruvail
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C5J1932 Strength 200 MG			Reference Product Lot # 9950321 Strength 200 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
1	10.3		6.5	15.8		9.7
2	21.2		12.6	30.2		4.2
4	38.1		7.9	58.3		1.9
6	55.0		4.7	79.9		1.8
8	68.7		3.9	92.5		1.6
10	78.7		3.7	98.3		1.0
24	100.5		1.9	104.7		1.4

JUN 2 5 1997

Ketoprofen Extended Release	Elan Pharmaceutical
200 mg Capsules	Gainesville, Georgia
ANDA # 74-879	Submission Date:
Reviewer: Man M. Kochhar	November 25, 1996

Review of Correspondence, ANDA # 74-879

Background:

1.The firm has requested that the Division of Bioequivalence reconsider the dissolution specifications. The firm is requesting five time points instead of six time points.

Comments:

1. The previous tentative dissolution specifications required six time points as follows:

Amount dissolved

1 hour	NLT [% and not more than [%
2 hours	NLT % and not more than %
4 hours	NLT % and not more than %
6 hours	NLT % and not more than %
10 hours	NLT % and not more than %
24 hours	NLT %

2. The tentative dissolution specifications can be reconsidered to have five time points as suggested by the firm. USP XXIII monographs allows five time points for extended release tablets or capsules. The time points should be as follows:

1 hour	NLT [% and not more than [%
2 hours	NLT % and not more than %
4 hours	NLT % and not more than %
6 hours	NLT % and not more than %
10 hours	NLT %

3. The firm should be allowed to conduct dissolution using 5 time points as mentioned in comment # 2.

RECOMMENDATIONS:

1. The fasting, non-fasting, and multiple-dose bioequivalence studies conducted by Elan Labs on its Ketoprofen Extended Release, 200 mg capsules, lot # C5J1932, comparing it to Oruvail capsules, 200 mg, lot # 9950321, manufactured by Wyeth Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules

acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules are bioequivalent to the reference product Oruvail 200 mg capsules manufactured by Wyeth Ayerst.

2. The <u>in vitro</u> test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

	Amount Dissolved
1 Hours	not less than [% and not more than [%
2 Hours	not less than % and not more than %
4 Hours	not less than % and not more than %
6 Hours	not less than % and not more than %
10 Hours	not less than %]

The interim specifications are based on the further review of the dissolution data on the bio lot. The final dissolution specifications will be set upon review of the dissolution data on atleast 3 production batches.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing and the study is acceptable.

The firm should be informed of the new recommendations.

APPEARS THIS WAY
ON ORIGINAL

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 6/13/97
Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: /S/ Date: 6/25/97
Nicholas M. Fleischer, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/6-2-97;74-879 BIO Addendum

Table 7 . In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen ER
Dose Strength: 200 mg
ANDA No.: 74-879
Firm: Elan Labs
Submission Date: March 29, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 phosphate buffer, pH 7.2

		Sponsor's	Division of Bioequivalence
Specifications:	1 Hour	----	between % and %
	2 Hours between	%	between % and %
	4 Hours between	%	between % and %
	6 Hours between	%	between % and %
	10 Hours between	%	NLT %
	24 Hours NLT	%	

Reference Drug: Oruvail

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C5J1932 Strength 200 MG			Reference Product Lot # 9950321 Strength 200 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
1	15.8		9.7	10.3		6.5
2	30.2		4.2	21.2		12.6
4	58.3		1.9	38.1		7.9
6	79.9		1.8	55.0		4.7
10	98.3		1.0	78.7		4.1
24	104.7		1.4	100.5		4.1

Ipratropium bromide
0.02% Inhalation solution
NDA #75-111
Reviewer: J. Lee
75111W.497

JL 21 1997

Alpharma
Baltimore, MD
Submission date:
April 11, 1997

Review of a Request for Waiver

The sponsor has submitted an application for ipratropium bromide 0.02% inhalation solution and is requesting a waiver from in-vivo bioequivalence testing for their test product under 21 CFR 320.22 (b)(3). The sponsor has provided a comparison (attached) between their test product and Atrovent® 0.02% inhalation solution (Boehringer Ingelheim) with regard to conditions of use, active ingredient, dosage form, route of administration, and strength.

The drug product is intended for inhalation administration.

A qualitative/quantitative formulation comparison is provided below:

	Alpharma per 2.5 ml	Atrovent per 2.5 ml
Ipratropium bromide	0.02%	0.02%
Sodium chloride	mg	mg*
HCl	- -	- -
Water for injection		

*The sponsor estimated that the brand product contained mg NaCl based on measurement of the osmolalities: Alpharma mOsmol
Atrovent mOsmol

Agency records indicate, however, that Atrovent contains mg of NaCl per 2.5ml of solution.

Comment:

1. The test and reference products are qualitative and quantitively the same within the guidelines of 'sameness' in OGD's Inactive Ingredients Guide.

Recommendation:

1. The Division of Bioequivalence agrees that the information submitted by the sponsor demonstrates that ipratropium bromide 0.02% inhalation solution falls under 21 CFR 320.22 (b)(3) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be

granted. Alpharma's ipratropium bromide 0.02% inhalation solution is deemed bioequivalent to Atrovent® 0.02% inhalation solutionmanufactured by Boehringer Ingelheim.

/S/ 7/21/97

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 7/21/1997

JLee/jl/07-21-97

Section IV

Information demonstrating that the proposed product is the same as the listed product.

	LISTED DRUG	**PROPOSED DRUG**
	Atrovent® 0.02%	Ipratropium Bromide
	Inhalation Solution	Inhalation Solution, 0.02%
	Boehringer Ingelheim	Alpharma
Conditions of use:	Indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.	
Active Ingredient:	ipratropium bromide	ipratropium bromide
Dosage Form:	solution	solution
Route of Administration:	inhalation	inhalation
Strength:	0.02%	0.02%

SEP 20 1997

Ketoprofen Extended Release
200 mg Capsules
ANDA # 74-879
Reviewer: Man M. Kochhar

Elan Pharmaceutical
Gainesville, Georgia
Submission Date:
September 9, 1997
Aug 20, 1997

Amendment to the Review of Correspondence, ANDA # 74-879

Background:

The firm has requested that the Division of Bioequivalence reconsider the dissolution specifications. The firm's specifications are based upon three recently manufactured lots.

Comments:

1. The firm has provided the dissolution profiles of three new lots along with the bio-batch lot.

2. The new dissolution specifications are based upon the three recently manufacture lots and the bio-batch lot which is approximately 18 months old. The specifications suggested by the firm are acceptable to the Division of Bioequivalence. The specifications are as follows:

	Amount dissolved
1 hour	NLT ⌜ % and not more than ⌜ %
2 hours	NLT % and not more than %
4 hours	NLT % and not more than %
8 hours	NLT % and not more than %
16 hours	NLT %

3. The firm should be allowed to conduct dissolution using 5 time points as mentioned in comment # 2.

RECOMMENDATIONS:

1. The fasting, non-fasting, and multiple-dose bioequivalence studies conducted by Elan Labs on its Ketoprofen Extended Release, 200 mg capsules, lot # C5J1932, comparing it to Oruvail capsules, 200 mg, lot # 9950321, manufactured by Wyeth Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules are bioequivalent to the reference product Oruvail 200 mg capsules manufactured by Wyeth Ayerst.

2. The in vitro test results are acceptable. The dissolution

testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

	Amount Dissolved
1 Hours	not less than [% and not more than [%
2 Hours	not less than % and not more than %
4 Hours	not less than % and not more than %
8 Hours	not less than % and not more than %
16 Hours	not less than %

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing and the study is acceptable.

The firm should be informed of the new recommendations.

APPEARS THIS WAY
ON ORIGINAL

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 9/19/97
Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: /S/ Date: 9/20/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMKochhar/mmk/9-19-97; BIO Addendum

Table 1 . In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen ER
Dose Strength: 200 mg
ANDA No.: 74-879
Firm: Elan Labs
Submission Date: April 1, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 phosphate buffer, pH 7.2

Specifications:			
1 Hour	between	%
2 Hours	between	%
4 Hours	between	%
8 Hours	between	%
16 Hours	NLT %	

Reference Drug: Oruvail
Assay Methodology:

APPEARS THIS WAY
ON ORIGINAL

KETOPROFEN EXTENDED RELEASE CAPSULES 200 MG

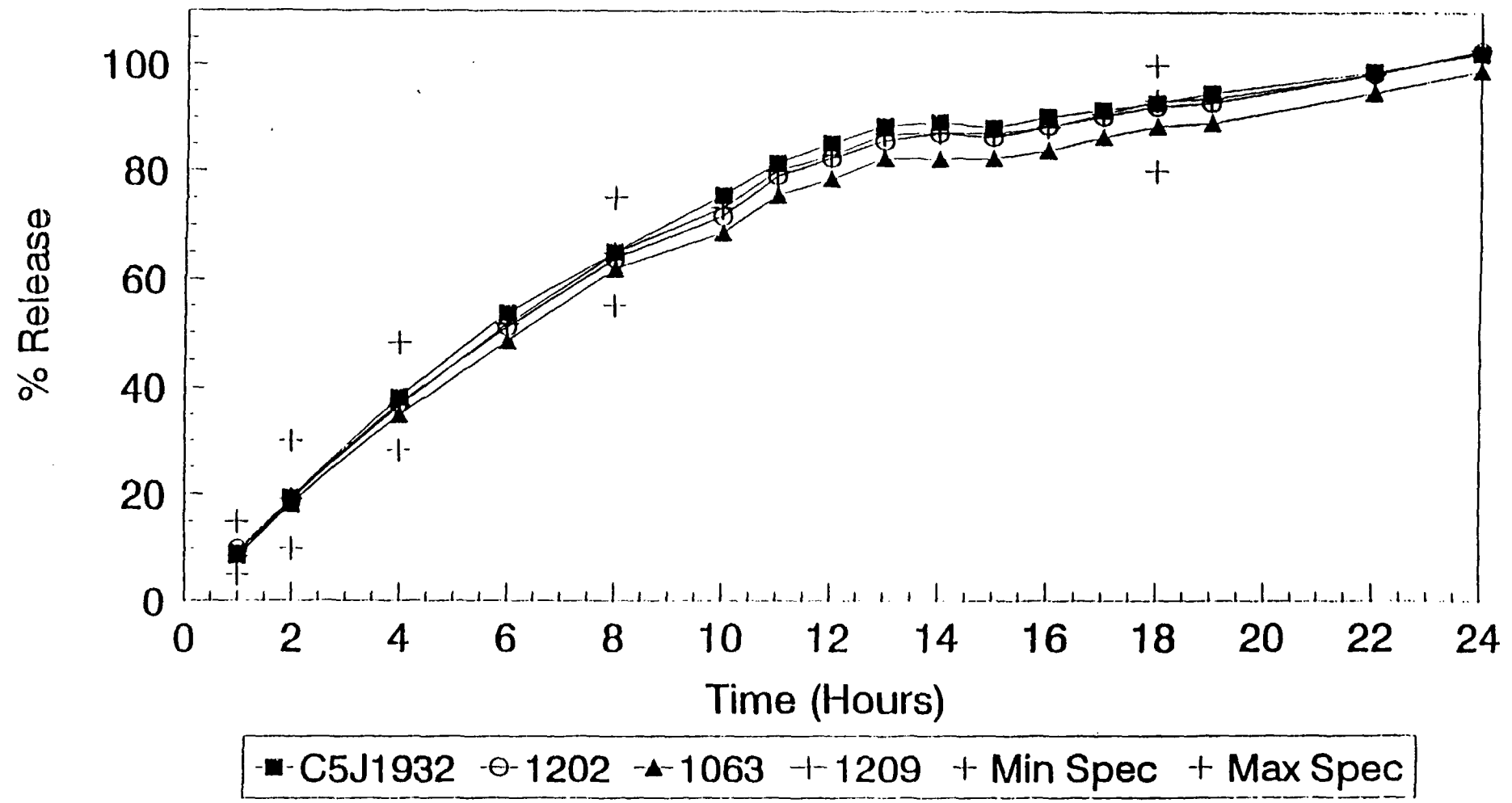
Lot No.	Mfg. Date	Dissolution Results																
		Hours	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**22**	**24**
C5J 1932 (ANDA Batch)	10-95	S1																
		S2																
		S3																
		S4																
		S5																
		S6																
		Mean	9.1	19.28	38.1	53.6	64.9	75.4	81.5	85.3	88.6	89.3	88.3	90.3	91.6	93.0	94.8	98.19	102.3
		SD	1.0	1.1	1.4	1.6	3.1	1.6	2.8	1.2	1.7	1.5	1.2	1.2	0.9	1.5	1.3	1.4	1.9
		CV	11.4	5.6	3.6	2.9	4.7	2.1	3.5	1.4	1.9	1.7	1.3	1.4	1.0	1.6	1.3	1.4	1.9
		Hours	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**22**	**24**
DD 1209	5-19-97	S1																
		S2																
		S3																
		S4																
		S5																
		S6																
		Mean	8.48	19.0	36.6	51.4	64.7	73.1	80.0	83.0	86.9	87.3	87.2	88.4	90.8	93.4	93.8	98.5	103.0
		SD	1.2	1.6	1.7	1.7	1.7	1.4	2.0	1.7	2.6	1.5	0.7	1.1	1.3	2.3	1.1	0.4	1.3
		CV	14.4	8.2	4.8	3.3	2.6	1.9	2.5	2.1	3.0	1.7	0.8	1.3	1.4	2.4	1.2	0.4	1.5

KETOPROFEN EXTENDED RELEASE CAPSULES 200 MG

Lot No.	Mfg Date	Dissolution Results																
		Hours	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**22**	**24**
DD 1202	4/29/97	S1																
		S2																
		S3																
		S4																
		S5																
		S6																
		Mean	9.85	19.15	37.0	50.9	63.7	71.5	79.0	82.4	85.7	87.2	86.4	88.5	90.4	92.3	93.0	98.5	102.7
		SD	1.4	1.1	1.4	1.0	1.3	1.0	0.5	0.8	1.9	1.0	0.8	1.3	1.2	1.2	1.5	1.4	0.9
		CV	14.6	5.7	3.9	2.0	2.1	1.3	0.7	1.0	2.2	1.2	1.0	1.4	1.4	1.3	1.6	1.4	0.9
		Hours	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**22**	**24**
DD 1063	4-23-97	S1																
		S2																
		S3																
		S4																
		S5																
		S6																
		Mean	8.64	18.22	34.8	48.3	61.8	68.5	75.4	78.5	82.40	82.3	82.4	83.9	86.5	88.6	89.3	94.9	99.1
		SD	0.8	0.9	1.9	2.4	3.9	2.5	2.4	2.7	2.6	2.1	1.5	1.3	1.4	0.9	0.9	0.7	1.8
		CV	9.5	4.7	5.4	5.0	6.3	3.7	3.2	3.4	3.2	2.6	1.9	1.5	1.7	1.0	1.0	0.7	1.8

Ketoprofen Extended-release Capsules 200mg

Mean Dissolution Profile with Proposed Specifications



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Ketoprofen
200 mg ER Capsule
ANDA 74-879
Reviewer: Pradeep M. Sathe, Ph.D.
WP #74879DO.n97

Elan Pharmaceutical Research
Gainsville, Georgia-30504
Submission Date:
October 30, 1997,
November 25, 1997

REVIEW OF THE DISSOLUTION DATA AND TARGET COMPOSITION

I.BACKGROUND: This consult review refers to ANDA 74-879 submitted to the Division of Bioequivalence on March 29, 1996 and the subsequent dissolution amendments submitted on August 20, 1997 and September 9, 1997, for the 200 mg Ketoprofen ER capsule formulation. The Division reviewed the ANDA and the dissolution information and in a review dated September 20, 1997, set the following dissolution specifications:

1 hour : Not less than [redacted] % and Not more than [redacted] %
2 hour : Not less than [redacted] % and Not more than [redacted] %
4 hour : Not less than [redacted] % and Not more than [redacted] %
8 hour : Not less than [redacted] % and Not more than [redacted] %
16 hour : Not less than [redacted] %

II.THE ISSUE: Ketoprofen Extended-Release Capsules 200 mg are manufactured by [redacted]

III.THE DISSOLUTION: The following methodology was used for the comparative dissolution of the bio-study lot #C5J1932 and lot #DD1212 (the closest target composition lot).

Apparatus: USP XXIII Apparatus 2 (paddle)
Speed: 50 rpm
Medium: Phosphate buffer, pH 7.2
Volume: 900 ml
Q: 1 hour : Not less than % and Not more than %
2 hour : Not less than % and Not more than %
4 hour : Not less than % and Not more than %
8 hour : Not less than % and Not more than %
16 hour : Not less than %

A. RESULTS OF THE DISSOLUTION TESTING : The dissolution results are given in Table 3.

IV.COMMENTS :

1. The Lot #DD1212 composition closely resembles the firm's proposed target composition.

2. The mean dissolutions and co-efficients of variation of the bio-studied lot #C5J1932 compare closely with the approximate target lot #DD1212.

3. The dissolutions of both lots #C5J1932 and #DD1212, comply with the previously set dissolution specifications.

V.RECOMMENDATIONS:

1. The dissolution testing data conducted by on its Ketoprofen ER capsule, lot #DD1212 is acceptable.

2. Firm's proposed target composition for the Ketoprofen ER capsule is acceptable and deemed equivalent to the bio-study lot composition.

/S/ 12/2/97

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG /S/ 12/2/97
FT INITIALED BY YCHUANG

Concur: /S/ 12/2/97

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence.

Table 3. In-Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen
Dose Strength: 200 mg ER Capsule
ANDA No.: 74-879
Firm: Elan Pharmaceutical Research Inc.
Submission Date: November 18, 1997
Units Used: 6 Assay Method:

I. Conditions for Dissolution Testing:

Apparatus: USP XXIII Apparatus 2 (paddle)
Speed: 50 rpm
Medium: Phosphate buffer, pH 7.2
Volume: 900 ml
Q: 1 hour : Not less than % and Not more than %
2 hour : Not less than % and Not more than %
4 hour : Not less than % and Not more than %
8 hour : Not less than % and Not more than %
16 hour : Not less than %

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Bio-study Lot : C5J1932 Ketoprofen ER Capsule Strength (200 mg), (Rev.date:9/20/97)			Approximate Target Lot : DD1212 Ketoprofen Capsule Strength (200 mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
1	9.1		11.4	11.6		6.4
2	19.28		5.6	20.5		4.3
4	38.1		3.6	38.8		2.2
8	64.9		4.7	68.0		2.6
16	90.3		1.4	91.9		1.1

SEP 13 1996

Ketoprofen Extended Release
200 mg Capsules
ANDA # 74-879
Reviewer: Man M. Kochhar

Elan Pharmaceutical
Gainesville, Georgia
Submission Date:
March 29, 1996

Review of 3 Bioequivalence Study and Dissolution (Fasting, Non-fasting and Steady State)

OBJECTIVE:

The objective of this study was to compare the single dose bioavailability of Elan Pharmaceutical and Wyeth Ayerst (Oruvail 200 mg) extended release capsules in healthy subjects under fasting, non-fasting and steady state conditions.

INTRODUCTION:

Ketoprofen is a nonsteroidal anti-inflammatory drug with analgegic and antipyretic properties. Ketoprofen is a racemate with only S enantiomer possessing pharmacological activity. It is a white, odorless, nonhygroscopic powder and is freely soluble in ethanol, chloroform,acetone, ether, and strong alkali. Each capsule contains 200 mg of coated pellets of ketoprofen. The dissolution is pH dependent with optimum dissolution at pH 6.5 to 7.5.

Ketoprofen is rapidly absorbed, with peak plasma levels occuring within 0.5 to 2 hours. In the extended release capsules the plasma levels do not occur until approximately 2 to 3 hours. Peak plasma levels are usually reached 6 to 7 hours after dosing. Food intake reduces C_{max} and increases the mean time to peak concentration.

IN-VIVO STUDY:

The objective of this study was to compare the bioavailability of Elan and Wyeth Ayerst (Oruvail) ketoprofen extended release 200 mg capsules under i) fasting, ii) non-fasting and iii) steady state conditions. The bioequivalence study was conducted by [ ] under the supervision of [ ]

STUDY DESIGN:

Study # 1

FASTING

The study was designed as a randomized, open-label, single dose, two-period crossover bioequivalence study in 30 healthy volunteers. During each of the two periods, the subjects received a single ketoprofen extended release capsule in a fasting state

Study # 2

NON-FASTING

The study was designed as a single dose, 3-way crossover bioequivalence study in 30 healthy volunteers under fasting (test product) and non-fasting (test and reference) conditions.

Study # 3

MULTIPLE-DOSE

The study was designed as a multiple-dose, 2-way crossover bioequivalence study in 30 healthy volunteers under fasting conditions. For each of the two dosing phases, the formulations were administered each morning for 5 consecutive days.

Subjects:

Each of the three studies (fasting, non-fasting and steady state) employed thirty (30) healthy volunteers between the ages of 18-40, whose weight did not deviate by more than ±10% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for at least 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 10 hours before and 36 hours after the drug administration.

In a non-fasting study, Treatment C: Subjects fasted for 10 hours before dosing and 4 hours thereafter. Treatment D and E: Subjects fasted overnight until 20 minutes prior to their scheduled dosing times, when they were given a standard breakfast. Water intake was restricted until 1 hour after drug administration. Standard meals were provided at 4 and approximately 9 hours after dosing.

In a multiple dose study subjects fasted for 9 hours before dosing each day and continued fasting for 3 hours post-dose. For each of the 2 dosing phases, the drugs were administered each day for 5

consecutive days.

Methods:

The product and dosage employed in this study were as follows:

FASTING:

Treatment A. Test: One 200 mg capsule of ketoprofen extended release, lot # C5J1932 with 240 mL of water (Fasting).

Batch size: [ ] capsules, Expiry Date: n/a
Content Uniformity: 99.1% Potency: 98.9%

Treatment B. Reference: One 200 mg Oruvail capsule (Wyeth), lot # 9950321 with 240 mL of water (Fasting).
Content Uniformity:99.3% ; Exp. n/a
Potency: 100.2%

NON-FASTING:

Treatment C: One 200 mg keoprofen extended release capsule (test drug), lot #C5J1932 with 240 mL of water (fasting).

Treatment D: One 200 mg ketoprofen extended release capsule (test drug), lot #C5J1932 with 24 mL of water (non-fasting).

Treatment E: One 200 mg Oruvail capsule (reference drug), lot # 9950321 with 240 mL of water (non-fasting).

In a non-fasting regimens subjects fasted overnight until 20 minutes prior to their schedule dosing times, when they were given a standard breakfast.

MULTIPLE-DOSE:

Treatment F: One 200 mg Ketoprofen extended release capsule (test drug), lot #C5J1932 with 240 mL of water on Day 1, Day 2, Day 3, Day 4 and Day 5 (fasting).

Treatment G: One 200 mg Oruvail capsule (reference drug), lot # 9950321 with 240 mL of water on Day 1, Day 2, Day 3, Day 4 and Day 5 (fasting).

Ten (10) mL of venous blood were drawn into a heparinized Vacutainers at 0 hour, (predose) on Day 1 to 4 inclusive and at 0 hour, (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, and 36 hours on Day 5. The plasma was separated and promptly

frozen for analysis.

In a fasting and non-fasting studies 10 mL of blood was drawn into a heparinized Vacutainers at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, and 36 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: 1 week and 10 days for multiple dose study.

ANALYTICAL METHODOLOGY:

ASSAY VALIDATION:

Concentration of Ketoprofen (mcg/mL)

DATA ANALYSIS:

Statistical significance of differences due to treatments, study days, dosing sequence, subjects within sequence, in plasma ketoprofen concentrations at each sampling time and its pharmacokinetic parameters were determined by analysis of variance (ANOVA) using Statistical Analysis Systems (SAS) general linear model (GLM) procedure. 90% confidence intervals (two one-sided t-test) were calculated for ketoprofen pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

STUDY NUMBER 1

FASTING STUDY:

Treatment A & B

All thirty (30) subjects completed the crossover. The plasma samples from the 30 subjects were assayed for ketoprofen as per protocol. The results of the study comparing the bioavailability of ketoprofen (test) and Oruvail (reference) products are given in Table 1 and 2. The mean plasma ketoprofen concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Ketoprofen (N= 30)

Time (hours)	Elan's Ketoprofen Extended-Release 200 mg Capsule Lot # C5J1932 mcg/mL (SD)	Wyeth Ayerst's Oruvail 200 mg Capsule Lot # 9950321 mcg/mL (SD)	T/R
0.00	0.0	0.0	
0.5	0.11 (0.07)	0.03 (0.04)	3.66
1.0	0.25 (0.17)	0.14 (0.11)	1.78
1.5	0.42 (0.31)	0.29 (0.21)	1.44
2.0	0.72 (0.59)	0.52 (0.40)	1.38
3.0	1.53 (1.07)	1.31 (0.96)	1.16
4.0	2.20 (1.03)	2.35 (1.24)	0.94
5.0	2.59 (0.55)	3.08 (0.94)	0.84
6.0	2.58 (0.72)	3.26 (0.98)	0.79
7.0	2.55 (0.79)	3.00 (1.17)	0.85
8.0	2.66 (0.90)	2.88 (0.99)	0.92
10.0	2.84 (0.68)	2.58 (0.76)	1.10
12.0	2.09 (0.47)	1.75 (0.56)	1.19
16.0	1.12 (0.41)	1.07 (0.32)	1.04
20.0	0.58 (0.41)	0.61 (0.25)	0.95
24.0	0.35 (0.22)	0.46 (0.25)	0.76
30.0	0.10 (0.03)	0.17 (0.11)	0.59
36.0	0.01 (0.03)	0.02 (0.04)	0.50

TABLE 2

A Summary of Pharmacokinetic Parameters for 30 Subjects (SD)

Parameters	Elan's Ketoprofen ER Mean (SD)	Wyeth's Oruvail Mean (SD)	T/R	90% Confidence Interval
AUC_{0-36} mcg.hr/mL	37.07 (5.9)	37.6 (7.0)	0.98	96; 100
AUC_{inf} mcg.hr/mL	37.78 (6.0)	38.59 (6.9)	0.98	96; 100
C_{max} mcg/mL	3.27 (0.6)	3.69 (1.1)	0.89	82; 96
T_{max} hours	7.07 (2.5)	6.20 (1.8)	1.14	
$t_{1/2}$ hours	4.27 (1.1)	5.33 (1.3)	0.80	

K_{el}	0.1723 (0.04)	0.1373 (0.03)	1.25	
	(CV%)			
Ln AUC_{0-36} mcg.hr/mL	3.60 (1.2)	3.61 (1.2)	0.99	97; 101
Ln AUC_{inf} mcg.hr/mL	3.61 (1.2)	3.63 (1.4)	0.98	96; 100
Ln C_{max} mcg/mL	1.17 (12.8)	1.23 (13.1)	0.90	84; 97

The ketoprofen AUC_{0-36} and AUCinf produced by Elan's formulation is 1.4% lower and 2.1% lower respectively than the reference drug. The C_{max} is 11.4% lower than the reference. The Tmax was 14% higher for the test drug. The t1/2 and Kel differ by 19.9% and 25.5% respectively. The 90% confidence intervals for log-transformed parameters were 97 to 101 for Ln AUCo-t, 96 to 100 for LnAUCinf and 84 to 97 for Ln Cmax.

The 90% confidence intervals for untransformed ketoprofen AUCo-t, AUCinf and C_{max} were well within 80 to 120 in a fasting study.

The ketoprofen concentration/time profiles of the two products showed significant differences at 0.5, 1.0, 1.5, 2, 24, 30 and 36 hours.

No serious adverse effects were experienced by any subject during the study.

STUDY NUMBER 2

NON-FASTING STUDY:

Treatment C, D & E

All of the 30 subjects enrolled in the study completed the crossover. In treatment C subjects fasted for 10 hours before dosing and 4 hours thereafter. In treatment D and E, subjects fasted overnight until 20 minutes prior to their schedule dosing times, when they were given a standard breakfast. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of ketoprofen are given in Table 3 and 4. The mean plasma ketoprofen concentrations are given in Figure 2.

TABLE 3

Mean Plasma Concentration of Ketoprofen (N=30)
(Non-Fasting)

Time Hours	Elan's Ketoprofen ER 200 mg Capsule mcg/mL (SD)			Wyeth's Oruvail 200 mg Capsule mcg/mL (SD)	T/R
	Fasting Treat. C	Non-fasting Treat. D	C/D	Non-Fasting Treat. E	D/E
0.5	0.12 (0.08)	0.00 ( )	0.00	0.00 ( )	0.00
1.0	0.28 (0.15)	0.01 (.03)	28.00	0.01 (.03)	1.00
1.5	0.41 (0.20)	0.04 (.04)	10.00	0.04 (.04)	1.00
2.0	0.62 (0.34)	0.09 (.07)	6.88	0.15 (.22)	0.6
3.0	1.36 (0.81)	0.28 (.26)	4.85	0.47 (.78)	0.59
4.0	2.19 (0.88)	0.75 (.77)	2.92	1.00 (1.25)	0.75
5.0	2.84 (0.94)	1.74 (1.52)	1.63	2.04 (1.64)	0.85
6.0	2.98 (1.00)	2.98 (1.88)	1.00	3.57 (2.02)	0.83
7.0	2.77 (0.92)	3.75 (1.69)	0.74	4.71 (2.07)	0.80
8.0	2.67 (0.92)	4.12 (1.85)	0.65	4.87 (1.82)	0.84
10.0	2.94 (0.96)	3.40 (1.77)	0.86	3.54 (1.47)	0.96
12.0	2.34 (0.63)	2.51 (1.35)	0.93	2.18 (1.18)	1.15
16.0	1.19 (0.50)	1.03 (0.55)	1.15	0.75 (0.48)	1.37
20.0	0.62 (0.29)	0.54 (0.39)	1.15	0.44 (0.20)	1.23
24.0	0.38 (0.22)	0.29 (0.22)	1.31	0.23 (0.26)	1.26
30.0	0.12 (0.11)	0.06 (0.06)	2.00	0.05 (0.07)	1.20
36.0	0.03 (0.06)	0.01 (0.02)	3.00	0.01 (0.03)	1.00

TABLE 4

A SUMMARY OF PHARMACOKINETIC PARAMETERS FOR 30 SUBJECTS
Non-Fasting

Parameters	Elan's Ketoprofen ER 200 mg Capsule Mean (SD)		Wyeth's Oruvail 200 mg Capsule Mean (SD)	T/R Treat.D/ Treat.E
	Fasted Treat.C	Fed Treat.D	Fed Treat.E	
AUC_{0-36} mcg.hr/mL	39.57 (8.9)	39.29 (13.3)	38.98 (8.4)	1.01
AUC_{inf} mcg.hr/mL	40.46 (9.1)	39.82 (13.4)	39.44 (8.3)	1.01
C_{max} mcg/mL	3.61 (1.0)	5.13 (1.7)	5.97 (1.7)	0.86

T_{max} hours	7.13 (2.4)	7.83 (2.4)	7.73 (1.4)	1.01	
$t_{1/2}$ hours	**4.49 (1.3)**	**3.54 (0.6)**	**3.27 (0.7)**	**1.08**	
K_{el} 1/hour	0.1626 (.03)	0.2018 (.03)	0.2217 (.04)	0.91	
					GEOMETRIC Mean Ratio
Ln AUC_{0-36} mcg.hr/mL	**3.66 (.22)**	**3.67 (.26)**	**3.64(.23)**	**1.01**	**1.03**
Ln AUC_{inf} mcg.hr/mL	3.68 (.22)	3.68 (.26)	3.65 (.23)	1.01	1.03
Ln C_{max} mcg/mL	1.26 (.26)	1.63 (.27)	1.73 (.33)	0.94	0.89

The ketoprofen AUCo-t and AUCinf produced by Elan's formulation is 1.87% lower and 0.96% higher respectively than the reference drug. The Cmax is 14% lower than the reference. The Tmax is 1.3% higher than the reference. Kel and t1/2 differ by 8.9% and 8.25%, respectively

Plasma concentrations were very similar at all time points except at 2, 3, and 4 hours following a dose of test and reference

The ratios of means for the untransformed parameters, for the AUC0-t, AUCinf and Cmax were 1.01, 1.01 and 0.86, respectively. Mean Tmax were practically same for test and reference products.

The geometric mean ratios for log transformed data were 1.03 for AUCo-t, 1.03 for AUCinf and 0.89 for Cmax.

There were no serious adverse effects reported during the study.

STUDY NUMBER 3

MULTIPLE-DOSE STUDY:

All 30 subjects completed the study. For each of the 2 dosing phases, the drug was administered each morning at approximately 7:30 am for five consecutive days. The subjects fasted for 9 hours before dosing until three hours after dosing. Ten (10) mL of blood were obtained in a vacutainer with heparin just prior to the first, second, third, fourth and fifth dose and then at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24 and 36 hours after the fifth dose. The results of the study comparing the bioavailability of

ketoprofen test and reference products are given in Table 5 and 6. The mean plasma concentrations of ketoprofen are shown in Figure 3.

TABLE 5

Mean Plasma Concentration of ketoprofen on Day 5 (N=30)
Multiple-Dose Study

Time (hours)	Elan's Ketoprofen ER 200 mg Capsules mcg/mL (SD)	Wyeth's Oruvail 200 mg Capsules mcg/mL (SD)	T/R
Pre Day 3	0.43 (77)	0.41 (117)	1.05
Pre Day 4	0.47 (131)	0.49 (129)	0.96
Pre Day 5	0.46 (.26)	0.50 (.28)	0.92
0.5	0.58 (.32)	0.53 (.24)	1.09
1.0	0.68 (.36)	0.59 (.26)	1.15
1.5	0.75 (.38)	0.68 (.27)	1.10
2.0	0.91 (.48)	0.82 (.31)	1.10
3.0	1.40 (.69)	1.34 (.72)	1.04
4.0	2.13 (.87)	2.21 (1.1)	0.96
5.0	2.97 (1.1)	3.07 (.92)	0.97
6.0	3.41 (1.3)	3.96 (1.2)	0.86
7.0	3.22 (1.3)	4.07 (1.5)	0.79
8.0	3.23 (1.1)	3.87 (1.4)	0.83
10.0	3.61 (1.0)	3.34 (.90)	1.08
12.0	2.90 (.71)	2.42 (.72)	1.19
16.0	1.43 (.40)	1.20 (.39)	1.19
20.0	0.68 (.26)	0.67 (.28)	1.01
24.0	0.38 (.17)	0.40 (.19)	0.95
36.0	.04 (.05)	0.05 (.06)	0.80

TABLE 6

A Summary of Pharmacokinetic Parameters for 30 subjects
Multiple-Dose Study

Parameters	Elan's Ketoprofen ER (CV%)	Wyeth's oruvail (CV%)	T/R	90% Confidence Intervals
AUC_{0-24} mcg.hr/mL	44.88 (8)	44.29 (9)	1.01	98; 105
C_{max} mcg/mL	4.17 (17)	4.53 (17)	0.92	84; 99
T_{max} hours	8.53 (21)	7.60 (20)	1.12	
Kel 1/hr	0.1645 (26)	0.1600 (18)	1.03	
t1/2 hours	4.42 (20)	4.65 (21)	0.95	
Ln AUC_{0-24} mcg.hr/mL	3.78 (2)	3.77 (2)	1.00	97; 105
Ln C_{max} mcg/mL	1.39 (12)	1.47 (13)	0.94	85; 99
Cmin mcg/mL	0.335 (35)	0.351 (32)	0.95	
FLUCI*	2.03 (21)	2.27 (20)	0.89	
FLUC2**	14.41 (59)	15.49 (45)	0.93	
FLUC3***	15.41 (60)	16.45 (55)	0.94	
FLUC4****	13.16 (54)	14.76 (56)	0.89	

*FLUC **(Cmax/Cmin)/Cav**
** FLUC (Cmax-Cmin)/Cmin
*** FLUC Cmax/Cmin
**** FLUC Cmax/C24Hr

All thirty (30) subjects completed the study. The pre-drug plasma ketoprofen concentrations were determined for each subject on Day 5. The ketoprofen AUCo-24, produced by Elan's formulation is 1.33% higher than the reference drug. The Cmax for test formulation was 7.9% lower than the reference drug. The ratio of Cmin was 0.95 and

Cmin for the test drug was 0.335 mcg/mL and for reference drug it was 0.351 mcg/mL. The degree of fluctuation was comparable for both products.. ANOVA were performed on the plasma ketoprofen concentrations at each of the 15 sampling times. The confidence intervals for log transformed AUC0-24 and Cmax were within the limits of 80% to 125%. The untransformed 90% confidence interval for Cmax was 84 to 99 and for AUC0-24 was 98 to 105.

On the basis of multiple-dose in vivo bioavailability data it is determined that Elan's ketoprofen extended release 200 mg capsules are bioequivalent to Wyeth Ayerst's Oruvail 200 mg capsules.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (Paddle) at 50 rpm. Results are presented in Table 7.
The batch size was [ ] capsules

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

FASTING (STUDY # 1)

Treatments A and B

1. All thirty volunteers completed the study and data from all subjects were assayed as per the protocol, comparing the plasma concentrations from Elan's ketoprofen extended release, 200 mg capsules to that of reference (Oruvail), 200 mg capsules manufactured by Wyeth Ayerst.

The ketoprofen AUC_{0-36}, AUC_{inf} and C_{max} of Elan's formulation were within the range comparable to reference values. The mean plasma ketoprofen concentration-time profiles showed significant differences at 0.5, 1.0, 1.5, 2, 30 and 36 hours.

2. Analysis of variance indicated no statistically significant treatment or sequence differences for AUC_{0-36}, AUC_{inf} and C_{max}. The 90% confidence intervals are well within 80% to 125% for all the log-transformed AUC and Cmax.

3. No serious side effects were observed which required the removal of any volunteer.

4. The in vitro dissolution testing conducted on both the test and reference products is acceptable.

5. The lots of test and reference products employed in the in vitro

dissolution test were identical to those employed in the in vivo bioequivalence study.

6. The in vivo fasting bioequivalence study and in vitro dissolution testing are acceptable.

NON-FASTING (STUDY # 2)

Treatments C, , D and E

1. The ratios for AUCo-24, AUCinf and Cmax of the test and reference formulations were 1.01, 1.01 and 0.86 respectively. The ratio for these parameters were well within the limits set by the Division of Bioequivalence. Plasma ketoprofen data showed no statistically significant differences in products for any of the calculated pharmacokinetic parameters.

2. The mean maximum concentration for the test formulation given with food was 29% higher than under fasting conditions. AUC was practically same.

3.The geometric mean ratios for AUCo-t, AUCinf and Cmax were 1.01, 1.01 and 0.89 respectively.

4. The Elan's ketoprofen extended release and Wyeth Ayerst's Oruvail showed comparable bioavailability for AUC and Cmax under non-fasting conditions. The ratios of the computed parameters AUC were almost identical and for Cmax it was 0.86.

5. No serious adverse events were recorded during this period which resulted in the withdrawal of any subject.

MULTIPLE-DOSE (STUDY # 3)

Treatment F and G

1. All thirty subjects completed the study. The AUC and Cmax of the test formulation were 1.33% higher and 7.9% lower respectively than the corresponding reference product. The confidence intervals for LN transformed Cmax and AUC0-24 were within the limits of 80 to 125. The confidence intervals for untransformed AUC was 98 to 105 and for Cmax was 84 to 99.

3. The Cmin was practically same for both products and the degree of fluctuation was acceptable to the Division of Bioequivalence. The study showed that steady state was achieved.

4. The multiple-dose study is acceptable.

DEFICIENCIES: None

RECOMMENDATIONS:

1. The fasting, non-fasting, and multiple-dose bioequivalence studies conducted by Elan Labs on its Ketoprofen Extended Release, 200 mg capsules, lot # C5J1932, comparing it to Oruvail capsules, 200 mg, lot # 9950321, manufactured by Wyeth Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules are bioequivalent to the reference product Oruvail 200 mg capsules manufactured by Wyeth Ayerst.

2. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

	Amount Dissolved			
1 Hours	not less than	%	and not more than	%
2 Hours	not less than	%	and not more than	%
4 Hours	not less than	%	and not more than	%
6 Hours	not less than	%	and not more than	%
12 Hours	not less than	%		

This is a tentative dissolution specifications. As more results are available, the Division of Bioequivalence will issue the dissolution specifications of this product.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing and the study is approvable.

The firm should be informed of the recommendations.

/S/
Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 9/5/96

Concur: /S/ Date: 9/13/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/7-17-96; 8-14-96; 9-5-96; 74-879 BIO

Table 7 . In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen ER
Dose Strength: 200 mg
ANDA No.: 74-879
Firm: Elan Labs
Submission Date: March 29, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 phosphate buffer, pH 7.2
Specifications: 1 Hour between % and %
2 Hours between % and %
4 Hours between % and %
6 Hours between % and %
12 Hours Not Less Than %
Reference Drug: Oruvail

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C5J1932 Strength 200 MG			Reference Product Lot # 9950321 Strength 200 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
1	15.8		9.7	10.3		6.5
2	30.2		4.2	21.2		12.6
4	58.3		1.9	38.1		7.9
6	79.9		1.8	55.0		4.7
10	98.3		1.0	78.7		4.1
24	104.7		1.4	100.5		4.1

Ketoprofen Extended Release
200 mg Capsules
ANDA # 74-879
Reviewer: Man M. Kochhar

Elan Pharmaceutical
Gainesville, Georgia
Submission Date:
March 29, 1996

Addendum to ANDA # 74-879

Background:

1.In the dissolution Table 7 the result columns were reversed and thus need to be corrected.The test product results should be in the reference product column and reference product results should be in the test product column. Therefore, a new dissolution Table 7 is generated and this new table should replace the old Table 7.

2. The specifications in the Table 7 are correct. These specifications should also be included in the recommendation part of the original review.

RECOMMENDATIONS:

1. The fasting, non-fasting, and multiple-dose bioequivalence studies conducted by Elan Labs on its Ketoprofen Extended Release, 200 mg capsules, lot # C5J1932, comparing it to Oruvail capsules, 200 mg, lot # 9950321, manufactured by Wyeth Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and steady-state conditions the Elan's Ketoprofen Extended Release 200 mg Capsules are bioequivalent to the reference product Oruvail 200 mg capsules manufactured by Wyeth Ayerst.

2. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

	Amount Dissolved
1 Hours	not less than % and not more than %
2 Hours	not less than % and not more than %
4 Hours	not less than % and not more than %
6 Hours	not less than % and not more than %
10 Hours	not less than % and not more than %
24 Hours	not less than %

This is a tentative dissolution specifications. As more results are available, the Division of Bioequivalence will issue the dissolution specifications of this product.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution

testing and the study is approvable.

The firm should be informed of the new recommendations.

/S/

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ 10/23/96

Concur: /S/ Date: 10/24/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMKochhar/mmk/10-22-96;74-879 BIO Addendum

Table 7 . In Vitro Dissolution Testing

Drug (Generic Name): Ketoprofen ER
Dose Strength: 200 mg
ANDA No.: 74-879
Firm: Elan Labs
Submission Date: March 29, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 phosphate buffer, pH 7.2

		Sponsor's	Division of Bioequivalence
Specifications:	1 Hour	----	between % and %
	2 Hours	between %	between % and %
	4 Hours	between %	between % and %
	6 Hours	between %	between % and %
	10 Hours	between %	between % and %
	24 Hours	not less than %	not less than %

Reference Drug: Oruvail

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C5J1932 Strength 200 MG			Reference Product Lot # 9950321 Strength 200 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
1	10.3	[redacted]	6.5	15.8	[redacted]	9.7
2	21.2		12.6	30.2		4.2
4	38.1		7.9	58.3		1.9
6	55.0		4.7	79.9		1.8
10	78.7		4.1	98.3		1.0
24	104.7		4.1	104.7		1.4