CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-434

BIOEQUIVALENCE

Naltrexone Hydrochloride Tablets
50 mg
ANDA #75434
Reviewer: Carol Y. Kim
x:\new\firmsam\eon\ltrs&rev\75434SD.898.doc

Eon Labs Manufacturing, Inc.
Laurelton, NY
Submission Date:
August 1, 1998
November 6, 1998

Review of a Bioequivalence Study and Dissolution Data

I. Introduction

Class: Opioate antagonist

RLD: Revia[R] Tablets, 50 mg, Du Pont Pharma (Previously known as Du Pont Merck)

Recommended Dose: Initial dose- 25 mg/day, Target dose- 50 mg/day

II. Objectives

Review of:

- Two-way crossover in vivo bioequivalence study comparing Eon Labs Manufacuring Inc.'s Naltrexone Hydrochloride Tablets 50 mg strength, to Du Pont Pharma's Revia[R] Tablets, 50 mg strength.
- Dissolution data for 50 mg tablets.

III. Background

Naltrexone is indicated in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opiods.

Naltrexone is rapidly and almost completely (about 96%) absorbed following an oral administration, but the drug undergoes extensive first-pass metabolism in the liver. The major metabolite is 6-β-naltrexol. Like naltrexone, 6-β-naltrexol has opiate antagonist activity. Peak plasma concentrations of naltrexone and 6-β-naltrexol usually occur within 1 hour following oral administration of tablets. Plasma concentration of 6-β-naltrexol generally range 1.5-10 times greater than those of naltrexone. Naltrexone is 21-28% protein bound. Naltrexone and its metabolites (unconjugated and conjugated) are excreted principally in urine via glomerular filtration.

IV. Protocol No. 970983: A single-dose, open-label, 2-way crossover randomized study under fasting conditions:

A. Study information

Study facility information:

Clinical Site:	Phoenix International Life Sciences Inc. St-Laurent, Quebec
Investigator:	Samuel Serfaty, M.D.
Analytical Site:	Phoenix International Life Sciences, Inc., St-Laurent, Quebec
Analytical Director:	
Study Dates:	Period #1: May 1, 1998 Period #2: May 15, 1998
Analysis Dates:	May 25, 1998 to July 10, 1998
Storage Period:	no > 69 days at -22°C

Study design:

Protocol No.:	970983
Design Type:	two-way crossover
Randomized:	Y
Single or Multiple dose:	single
No. of Treatment:	2
No. of Periods:	2
No. of Sequences:	2
Washout Period:	14 days

Subjects:

Normal Healthy Volunteers:	Y
IRB Approval:	Y
Informed Consent	Y
No. of Subjects Enrolled:	Entered: 40 males Completed: 39 males Excluded from analysis: 3 males
Age:	18-45 years
Inclusion/Exclusion Criteria:	listed in vol: 1.2, pages 2035-2036
Housing:	Evening prior to each drug administration until After 36 hour blood sample.

Treatment information:

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Naltrexone Tablet	Revia[R] Tablet
Strength:	50 mg	50 mg
Manufacturer:	Eon Labs Manufacturing Inc.	Du Pont Pharma

Lot No.:	#971001	#LD158A
Batch Size (ANDA/Full):		
Expiration Date:	TBE	4/99
Content Uniformity	99.8%	100.9%
Assay:	97.2%	98.2%
Dose Administered:	50 mg	50 mg
Length of Fasting:	overnight	overnight

Dosing:

Subjects fasted overnight before dosing and for at least 4 hours after dosing. Each oral dose was administered with 240 ml of water. Standard meals were provided at 4 and approximately 9 hours after dosing.

Blood Sampling:

Blood sample volume	5 ml
No. of time points	22
Time points:	0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hours post dose

The plasma blood samples were stored at –22°C until analysis

B. Study Results

1. Clinical

Drop-outs: Subject #30 was discontinued during period 1 in treatment group B due to medical events (nausea, vomiting, trembling left and right hand and sore stomach) requiring treatment. The medical Designate diagnosed that the subject was having gastritis with a remote association with the study drug.

Adverse events: From a total of 32 adverse events reported in association to the study drug, four adverse events (3 subjects) were possibly or probably drug related to the treatment group A and ten adverse events (6 subjects) for treatment group B. The remaining events were reported as remote association with the study drug. (vol. 1.2, pp.2292-2304) The common adverse events were headache, dizziness, nausea, and vomiting.

2. Analytical Analysis (The following section is not to be released under FOI)

Method:

Internal Standard:

Specificity: No interfering peaks noted in blank chromatograms (see vol. 1.5, p.3078)

Linearity: 0.2 -20.00 ng/ml for naltrexone and 2.00-200.00 ng/ml for 6-β-naltrexol, R^2 ranged from 0.9852 to 0.9993 for naltrexone and 0.9813 to 0.9997 for 6-β-naltrexol.

Sensitivity: LOQ=0.2 ng/ml (naltrexone), 2.00 ng/ml (6-β-naltrexol)

Quality Control (QC) Samples:	**Naltrexone**	**6-β-naltrexol**
High:	16.10 ng/ml	160.63 ng/ml
Mid:	7.04 ng/ml	70.28 ng/ml
Low:	0.60 ng/ml	6.02 ng/ml
Precision of QC Samples:	4.9-12.6 % CV within run	4.2-13.9 % CV within run
	5.6-16.4 % CV between run	8.6-13.8 % CV between run
Accuracy of QC Samples:	91.5 –101.1 % within run	90.3-104.0 % CV within run
	96.3-105.4 % between run	91.5-103.4 % CV between run

Stability in Plasma:

Freeze-thaw: 4 cycles

Short-term (bench top) at 20°C: 7.5 hours

Long term at –22°C: 169 days

Recovery:

Naltrexone	6-β-naltrexol	Internal standard: 57.1%
High (16.10 ng/ml): 60.4%	160.63 ng/ml: 67.0%	
Mid (7.04 ng/ml): 58.6%	70.28 ng/ml: 67.1%	
Low (0.60 ng/ml): 84.2%	6.02 ng/ml: 87.3	

Dilution Integrity: Prepared concentration in human plasma: 70.490 ng/ml (Naltrexon), 702.75 ng/ml (6-β-naltrexol)

Naltrexon: 1: 5 dilution (6 replicates)- %CV=5.7, accuracy=96.8%
1: 10 dilution (6 replicates)- %CV=6.9, accuracy=96.2%

6-β-naltrexol: 1: 5 dilution (6 replicates)- %CV=6.2, accuracy=92.5%
1: 10 dilution (6 replicates)- %CV=5.2, accuracy=87.4%

Reassays: There were at least 79 repeat assays (57 for naltrexone vs. 22 for 6-β-naltrexol) and 2 reasons for reassays: 1) anomalous sample value, 2) highest and/or lowest standards missing from the regression (vol 1.5, pp. 3021-3027 (T51, T52))

Protocal Deviations: Y (see vol 1.2, p. 2287)

Conclusion: **Analytical method is acceptable**

3. Pharmacokinetic/Statistical Analysis

As per study protocol, data were analyzed from only 36 subjects. Since subject #30 withdrew, subject #38 was substituted.

Mean Naltrexone and 6-β-naltrexol plasma levels of 36 subjects are summarized in Table 1.

Table 1: Mean Naltrexone and 6-β-naltrexol Plasma Concentrations following an oral dose of 50 mg for test and reference products (N=36)

	Naltrexone : Test Lot# 971001		Naltrexone: Reference Lot # LD158A		Ratio	6-β-naltrexol: Test Lot# 971001		6-β-naltrexol: Reference Lot# LD158A		Ratio
Time (hour)	Mean (ng/ml)	CV %	Mean (ng/ml)	CV %	T/R	Man (ng/ml)	CV %	Mean (ng/ml)	CV %	T/R
0.00	0.000	0.0	0.000	0.0	0	0.000	0.0	0.000	0.0	0
0.167	0.000	0.0	0.084	382.3	0	0.125	600.0	0.797	200.3	0.16
0.33	1.137	102.4	1.051	86.8	1.08	15.122	77.8	13.997	90.1	1.08
0.5	3.971	78.3	3.043	66.8	1.30	59.368	70.8	38.042	59.5	1.56
0.67	5.423	60.2	5.322	62.3	1.02	76.220	44.5	63.816	46.2	1.19
0.83	5.938	52.4	6.210	64.5	0.96	76.247	37.9	72.858	39.7	1.05
1	5.731	48.2	6.323	62.4	0.91	75.270	33.4	74.435	35.8	1.01
1.25	5.081	47.7	6.054	63.2	0.84	66.144	28.6	71.044	29.7	0.93
1.5	4.537	48.2	5.331	59.7	0.85	61.200	22.2	63.667	28.3	0.96
2	3.686	54.7	4.117	55.6	0.89	51.650	27.8	53.809	22.0	0.96
3	2.593	55.4	2.942	57.4	0.88	41.750	23.3	42.571	24.4	0.98
4	1.974	60.8	2.072	64.1	0.95	34.888	23.8	35.461	25.1	0.98
6	1.045	57.5	1.144	59.7	0.91	28.401	24.1	28.714	24.3	0.99
8	0.690	63.8	0.663	60.2	1.04	23.509	26.5	22.647	26.3	1.04
10	0.469	85.7	0.463	78.4	1.01	18.574	26.4	18.831	27.4	0.99
12	0.444	82.3	0.445	77.6	0.99	16.789	24.5	16.851	24.5	0.99
16	0.288	97.7	0.258	138.0	1.11	13.847	27.9	13.848	24.3	1.0
24	0.029	294.2	0.033	301.2	0.88	9.449	27.8	9.426	26.1	1.0
36	0.006	600.0	0.007	600.0	0.86	4.182	39.4	4.299	36.9	0.97
48	0.000	0.0	0.009	600.0	0	1.933	90.9	2.158	89.9	0.89
60	0.000	0.0	0.000	0.0	0	0.438	222.4	0.211	329.6	2.07
72	0.000	0.0	0.000	0.0	0	0.000	0.0	0.063	600.0	0
96	0.000	0.0	0.000	0.0	0	0.000	0.0	0.000	0.0	0

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for Naltrexone are shown in Table 2. The LS means of the log-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2: Test mean/Reference mean ratios of Naltrexone and 6-β-naltrexol pharmcokinetic parameters

	Naltrexone					6-β-naltrexol				
Parameter*	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]
AUCI	24.229	54.9	23.113	55.1	1.05	719.5	22.0	717.3	21.8	1.00
AUCT	21.773	57.4	23.199	64.1	0.94	653.7	24.1	654.4	23.6	0.99
CMAX	6.812	45.8	7.339	62.5	0.93	89.84	36.5	85.62	33.4	1.05
KE	0.20091	41.5	0.21714	43.3	0.93	0.053	21.9	0.05386	23.5	0.98
T ½	3.989	37.4	3.644	35.1	1.09	13.688	29.0	13.674	26.8	1.00
TMAX	0.941	38.0	1.077	27.7	0.87	0.910	37.4	1.046	27.9	0.87

*AUCT=ng*hr/ml, AUCI=Ng*hr/ml, TMAX=hr, CMAX=ng/ml
[1]Calculated by reviewer

Table 3: Geometric LSMeans and 90% confidence intervals for Naltrexone and 6-β-naltrexol Tablet

	Naltrexone		6-β-naltrexol		Naltrexone		6-β-naltrexol	
Parameter*	LS Means (test)	LS Means (ref)	LS Means (test)	LS Means (ref)	Low CI (%)**	Upper CI (%)**	Low CI (%)**	Upper CI (%)**
LAUCI	18.92	19.49	699	699	88.5	103.6	96.2	103.3
LAUCT	20.70	21.54	632	632	90.1	103.1	97.1	102.3
LCMAX	6.11	6.23	83.9	80.6	88.8	109.6	96.5	112.9

**Used natural log transformed parameter

Comments

1. Plasma concentration levels for 6-β-naltrexol are approximately 10 times higher than the parent drug.

2. Values of CMAX, AUCT, and AUCI mean ratios of Naltrexone and 6-β-naltrexol for the test product versus reference product administered under fasting conditions (ratio A/B) are within the acceptable range of 0.8-1.2.

3. There were no statistically significant period or sequence effects for any of the above parameters. ($p>0.05$) The pharmacokinetic parameters and 90% confidence intervals of Naltrexone and 6-β-naltrexol re-calculated by the reviewer were in good agreement with the values determined by the firm.

4. The mean (%CV) AUC_T/AUC_I ratios of Naltrexone were 91.30 (3.55), range 83.0 to 96.9, and 91.73 (3.76), range 82.8 to 96.8, for test and reference, respectively. The mean (%CV) AUC_T/AUC_I ratios of 6-β-naltrexol were 90.56 (5.22), range 68.7 to 96.6, and 90.43 (3.98), range 81.7 to 95.7, for test and reference, respectively.

5. AUCI could not be calculated for subject # 3,4,6,14,17,23,24,28, and #32 because subject Kel could not be determined. The reviewer concurs with this decision.

6. The 90% confidence intervals of log-transformed AUCT, AUCI, and CMAX ratios for Naltrexone and 6-β-naltrexol are all within 80-125% range.

V. Dissolution

Method of dissolution	USP 23, Apparatus II (paddles)
Speed	50 rpm
No. of Units Tested	12
Medium	Water
Temperature	37°C
Volume	900 ml
Specifications	NLT s dissolved in 60 minutes
Assay Methodology	
Reference Product	Du Pont Pharma's Revia[R] Tablet, 50 mg

Result of In Vitro Dissolution Profile Summary for Naltrexone 50 mg

Sampling Times (minutes)	Eon Manufacturing, Inc. Lot # #971001 **Strength: 50 mg**			Revia[R] Lot # #LD158A **Strength: 50 mg**		
	Mean %	Range %	%CV	Mean %	Range %	%CV
10	29.9		15.0	37.0		12.4
20	64.0		7.2	66.2		5.7
30	86.5		4.4	85.9		3.5
60	98.1		2.6	100.6		1.4
70	98.9		2.2	100.8		1.8

Composition of Eon's Naltrexone 50 mg Tablet (Not to Be Released Under FOI)

Components	**Mg/tablet**	**%w/w**
	Core	
Naltrexone Hydrochloride	**50.0**	16.2
Colloidal Silicon Dioxide,		
Lactose Monohydrate		
Crospovidone,		
Microcrystalline Cellulose,		
Magnesium Stearate,		
	Coated Tablets	
		Removed
Total	**308**	**100**

Comment

The firm conducted dissolution according to the procedure described in the OGD guidance. The dissolution data are acceptable.

VI. Recommendations

1. The single-dose bioequivalence study #970983 under fasting conditions, conducted by Eon Manufacturing Inc. on its Naltrexone Hydrochloride Tablet, 50 mg, lot #971001, comparing it to Revia[R] 50 mg, lot #LD158A, manufactured by Du Pont Pharma, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon Manufacturing Inc.'s Naltrexon Hydrochloride Tablet, 50 mg is bioequivalent to Du Pont Pharma's Revia[R] Tablet, 50 mg.

2. The dissolution method conducted by Eon Manufacturing Inc. on its Naltrexone Tablets, 50 mg, lot #971001, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 Apparatus II (paddles) at 50 rpm. The test should meet the following specification:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT BDA 10/6/98
FT INITIALLED BY BDAVIT Barbara David Date: 11/10/98

Concur Dale P. Conner Date: 11/12/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence