CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-434

BIOEQUIVALENCE

Naltrexone Hydrochloride Tablets
50 mg
ANDA #75434
Reviewer: Carol Y. Kim
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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 5.6-16.4 % CV between run	4.2-13.9 % CV within run 8.6-13.8 % CV between run
Accuracy of QC Samples:	91.5 –101.1 % within run 96.3-105.4 % between run	90.3-104.0 % CV within 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**

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