

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

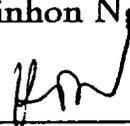
40281

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #40-280 & 40-281 SPONSOR : Endo Pharmaceuticals
DRUG & DOSAGE FORM : Hydrocodone Bitartrate/Acetaminophen Tablets
STRENGTH (s) : 7.5/500 mg, 7.5/650 mg, 10/650 mg, 5/500 mg and 7.5/750 mg

DISSOLUTION:	<input checked="" type="checkbox"/> Acceptable	<input type="checkbox"/> Not Applicable
WAIVER:	<input checked="" type="checkbox"/> Acceptable	<input type="checkbox"/> Not Applicable

REVIEWER: Hoainhon Nguyen	BRANCH: I
INITIAL: 	DATE: 2/13/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D.	BRANCH : I
INITIAL : 	DATE: 2/13/98

DIRECTOR: Dale Conner, Pharm.D.	
DIVISION OF BIOEQUIVALENCE	
INITIAL : 	DATE: 2/13/98

BIOEQUIVALENCY COMMENTS

ANDA: 40-280
40-281

APPLICANT: Endo Pharmaceuticals

DRUG PRODUCT: Hydrocodone Bitartrate/Acetaminophen Tablets USP,
7.5/500 mg, 7.5/650 mg, 10/650 mg, 5/500 mg and 7.5/750 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/s/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Hydrocodone Bitartrate/Acetaminophen Tablets USP
ANDA #40-280: 7.5/500 mg, 7.5/650 mg & 10/650 mg
ANDA #40-281: 5/500 mg & 7.5/750 mg
Reviewer: Hoainhon Nguyen
WP # 40280dw.o97

Endo Pharm.
Garden City, NY
Submission Date:
October 17, 1997

Review of Dissolution Data and Waiver Requests

The firm has submitted comparative dissolution data for the above test products and the corresponding RLD products, Mikart's Lortab® 7.5/500 mg Hydrocodone/Acetaminophen, Lorcet® Plus 7.5/650 mg, Lorcet® 10/650 mg, Knoll's Vicodin® 5/500 mg and Vicodin ES® 7.5/750 mg. The firm is requesting a waiver of *in vivo* bioequivalence requirements for the test products based on the dissolution data and the Therapeutic Equivalence rating "AA" of the drug product.

Dissolution Results: USP method and specifications

See the results at the end of the review.

Comments:

1. The dissolution data for the test product are acceptable.
2. The compositions of the test products are attached.

Recommendations:

1. The dissolution testing conducted by Endo Pharmaceuticals on its Hydrocodone Bitartrate/Acetaminophen Tablets, 7.5/500 mg, 7.5/650 mg, 10/650 mg, 5/500 mg and 7.5/750 mg, is 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 pH 5.8 phosphate buffer at 37 C using USP XXIII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

Not less than % of the labeled amount of Hydrocodone and Acetaminophen in the dosage form is dissolved in 30 minutes.

2. The Division of Bioequivalence agrees that the information submitted by Endo Pharmaceuticals demonstrates that its proposed Hydrocodone Bitartrate/Acetaminophen Tablets, 7.5/500 mg, 7.5/650 mg, 10/650 mg, 5/500 mg and 7.5/750 mg, fall under 21 CFR 320.22 (c) of the Bioavailability/Bioequivalence Regulations. The waiver of an *in vivo* bioequivalence study for the test products is granted. The test products are deemed bioequivalent, respectively, to currently approved Mikart's Lortab®, 7.5/500 mg, Lorcet®, 7.5/650 mg and Lorcet ES®, 10/650 mg, and Knoll's Vicodin®, 5/500 mg, and Vicodin ES®, 7.5/750 mg.

/S/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/

2/13/98

Concur: **/S/** Date: 2/13/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 40-280 and 281 (original, duplicate), HFD-652(Huang, Nguyen),
Drug File, Division File

Hnguyen/02-10-98/WP #40280dw.o97

Attachments: 5 pages

Test Product
Lot # LD165
Strength (mg) 10/650

Reference Product (Lorcet)
Lot # 950605F
Strength (mg) 10/650

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>100.5</u>		<u>(0.5)</u>	<u>100.5</u>		<u>(0.6)</u>
<u>20</u>	<u>101.5</u>		<u>(0.6)</u>	<u>100.8</u>		<u>(0.6)</u>
<u>30</u>	<u>101.9</u>		<u>(0.5)</u>	<u>100.8</u>		<u>(0.5)</u>
<u>45</u>	<u>103.8</u>		<u>(0.5)</u>	<u>100.9</u>		<u>(0.6)</u>

Test Product
Lot # LD169
Strength (mg) 5/500

Reference Product (Vicodin)
Lot # 10760465
Strength (mg) 5/500

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>100.6</u>		<u>(0.8)</u>	<u>71.2</u>		<u>(2.4)</u>
<u>20</u>	<u>100.9</u>		<u>(0.6)</u>	<u>79.2</u>		<u>(2.5)</u>
<u>30</u>	<u>101.3</u>		<u>(1.0)</u>	<u>82.1</u>		<u>(2.4)</u>
<u>45</u>	<u>101.4</u>		<u>(0.6)</u>	<u>85.6</u>		<u>(2.3)</u>

Test Product
Lot # LD170
Strength (mg) 7.5/750

Reference Product (Vicodin ES)
Lot # 10770595
Strength (mg) 7.5/750

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>100.9</u>		<u>(0.8)</u>	<u>81.7</u>		<u>(14.0)</u>
<u>20</u>	<u>101.3</u>		<u>(1.0)</u>	<u>99.4</u>		<u>(0.5)</u>
<u>30</u>	<u>101.5</u>		<u>(1.0)</u>	<u>98.9</u>		<u>(4.3)</u>
<u>45</u>	<u>101.7</u>		<u>(1.0)</u>	<u>100.2</u>		<u>(0.6)</u>

Hydrocodone Results:

Test Product
Lot # LD167
Strength (mg) 7.5/500

Reference Product (Lortab)
Lot # 951347L
Strength (mg) 7.5/500

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>100.6</u>		<u>(1.4)</u>	<u>98.6</u>		<u>(1.4)</u>
<u>20</u>	<u>101.0</u>		<u>(2.1)</u>	<u>99.4</u>		<u>(1.5)</u>
<u>30</u>	<u>101.1</u>		<u>(2.2)</u>	<u>99.4</u>		<u>(1.5)</u>
<u>45</u>	<u>101.3</u>		<u>(2.1)</u>	<u>99.4</u>		<u>(1.3)</u>

Test Product
Lot # LD164
Strength (mg) 7.5/650

Reference Product (Lorcet Plus)
Lot # 950488D
Strength (mg) 7.5/650

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>100.5</u>		<u>(1.5)</u>	<u>99.1</u>		<u>(1.6)</u>
<u>20</u>	<u>100.6</u>		<u>(1.5)</u>	<u>100.1</u>		<u>(1.1)</u>
<u>30</u>	<u>100.9</u>		<u>(0.9)</u>	<u>100.0</u>		<u>(1.1)</u>
<u>45</u>	<u>100.2</u>		<u>(0.9)</u>	<u>100.1</u>		<u>(1.1)</u>

Test Product
Lot # LD165
Strength (mg) 10/650

Reference Product (Lorcet)
Lot # 950605F
Strength (mg) 10/650

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>97.0</u>		<u>(2.2)</u>	<u>95.7</u>		<u>(2.7)</u>
<u>20</u>	<u>97.3</u>		<u>(1.8)</u>	<u>96.9</u>		<u>(0.8)</u>
<u>30</u>	<u>97.3</u>		<u>(1.6)</u>	<u>96.2</u>		<u>(1.5)</u>
<u>45</u>	<u>98.0</u>		<u>(2.3)</u>	<u>96.3</u>		<u>(1.2)</u>

Test Product
Lot # LD169
Strength (mg) 5/500

Reference Product (Vicodin)
Lot # 10760465
Strength (mg) 5/500

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>99.3</u>		<u>(1.8)</u>	<u>94.0</u>		<u>(2.7)</u>
<u>20</u>	<u>99.6</u>		<u>(2.5)</u>	<u>98.5</u>		<u>(3.2)</u>
<u>30</u>	<u>100.8</u>		<u>(2.1)</u>	<u>100.2</u>		<u>(3.1)</u>
<u>45</u>	<u>100.5</u>		<u>(2.5)</u>	<u>99.8</u>		<u>(1.8)</u>

Test Product
Lot # LD170
Strength (mg) 7.5/750

Reference Product (Vicodin ES)
Lot # 10770595
Strength (mg) 7.5/750

<u>Sampling Time (Min.)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>	<u>Mean % Dissol.</u>	<u>Range</u>	<u>(CV%)</u>
<u>10</u>	<u>98.5</u>		<u>(0.9)</u>	<u>89.3</u>		<u>(10.1)</u>
<u>20</u>	<u>99.0</u>		<u>(1.1)</u>	<u>98.4</u>		<u>(1.5)</u>
<u>30</u>	<u>98.7</u>		<u>(1.1)</u>	<u>98.2</u>		<u>(1.7)</u>
<u>45</u>	<u>99.1</u>		<u>(1.0)</u>	<u>98.2</u>		<u>(1.8)</u>

USP Specifications:

NLT % of both components in 30 minutes