

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

40281

CHEMISTRY REVIEW(S)

Division Approval Summary

ANDA #: 40-280 **DRUG PRODUCT:** Hydrocodone Bitartrate and Acetaminophen Tablets, USP
(7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg)

FIRM: Endo Pharmaceuticals, Inc.

DOSAGE: Tablets

STRENGTH: 7.5 mg/500 mg, 7.5 mg/650 mg and 10 mg/650 mg

cGMP STATEMENT/EIR UPDATE STATUS:

cGMP: GMP Certification (pages # 311-312) is Adequate
EER: Acceptable dated 11/19/97

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:

On 2/13/97 the Division of Bioequivalence issued a no comments letter to the firm.

METHODS VALIDATION(Including dosage form description):

Not required because it is a USP drug. Field analyzed the samples and satisfactory results are attached in the ANDA.

STABILITY(Conditions, Containers, methods):

Bio batch

Specifications

TEST	SPECIFICATION
Appearance	7.5/500: White, oval, convex tablet debossed with 'E725' on one side and scored on the other 7.5/650: White, oval, convex tablet debossed with 'E732' on one side and scored on the other 10/650: White, capsule shaped, convex tablet, debossed with 'E747' on one side and scored on the other
Assay: (Hydrocodone Bitartrate) (Acetaminophen))% for each active
Dissolution:	Q= % in 30 min for each active

Acetaminophen degradation Products		
4-Aminophenol	NMT	%
Each unknown	NMT	%
Total	NMT	%
Hydrocodone degradation Products		
Dihydromorphinone	NMT	%
Hydrocodone Diol	NMT	%
Each unknown	NMT	%
Total	NMT	%

Stability studies were done on the bio batch. Containers are the same as those listed in the container section (packaged in 100 count and 1000 count). Stability studies are in conformance with the FDA Guidelines.

LABELING REVIEW STATUS: Satisfactory dated 5/28/98.

STERILIZATION VALIDATION(If Applicable): N/A

BATCH SIZES:

BIO BATCH(identity #, DS source)

Batch #:

Batch size: for 7.5 mg/500 mg
 for 7.5 mg/650 mg
 for 10 mg/650 mg

NDS source:

Hydrocodone Bitartrate:

Acetaminophen:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)

Stability batch is the same as the bio batch

PROPOSED PRODUCTION BATCH

Same as bio batch sizes.

Process and equipment are the same as the demonstration batch. Reprocessing statement is also provided on page 572.

COMMENTS: Approvable

CHEMISTRY REVIEWER:

Radhika Rajagopalan, Ph.D.

DATE:

7/20/1998; 9/3/98

9/10/98

TEAM LEADER:

Brenda T. Arwine

DATE:

9/9/98

F/T by pah/9/10/98

ISI

9/10/98

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-280

3. NAME AND ADDRESS OF APPLICANT

Endo Pharmaceuticals Inc.
Attention: Andrew G. Clair, Ph.D.
500 Endo Blvd.
Garden City, NY 11530

4. LEGAL BASIS FOR SUBMISSION

Certifies to the best of their knowledge there are no patents that claim the listed drug product and referenced listed drug are not entitled to a period of marketing exclusivity. Paragraph II Certification statement is filed in page 9.

Listed Product: Mikart - Lortab® 7.5/500, ANDA 89-699
Mikart - Locet® Plus 7.5/650, ANDA 89-699
Mikart - Locet® 10/650, ANDA 81-223

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate
and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm: 10/17/97 - Original submission
11/19/97 - Response to Telephone call and
additional Information
3/11/98 - Amendment
5/5/98 - Amendment
5/26/98 - Amendment
6/23/98 - Amendment
8/24/98 - Amendment
8/28/98 - Fax amendment

FDA: 11/10/97- Acknowledgment letter
11/19/97- Telephone call by Greg Davis, FDA
01/02/98- Field analysis completed (letter)
2/13/98 - Bio. review, acceptable (waiver granted)
4/17/98 - Label review, deficiency
6/22/98 - Chemistry facsimile deficiency
7/27/98 - Phone call by Mrs. B. Arnwine
8/28/98 - Phone call by R. Rajagopalan

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
R

12. RELATED IND/NDA/DMF(s)**DMF**LoA); **DMF**

LoA). The rest are detailed under item 37.

13. DOSAGE FORM

Tablet

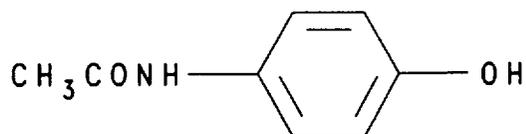
14. POTENCY

7.5 mg/500 mg

7.5 mg/650 mg & 10mg/650 mg

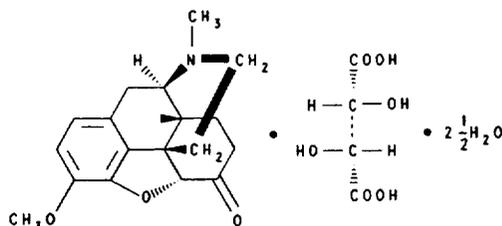
15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

 $C_8H_9NO_2$; M.W. = 151.16

4'-Hydroxyacetanilide. CAS [103-90-2]

Hydrocodone Bitartrate USP

 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$; M.W. = 494.504,5 α -Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Method validation not needed, product is USP. Field has analyzed samples and found methods to be satisfactory. DMFs are satisfactory. Labeling review satisfactory. Bio waiver granted.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable.

19. REVIEWER:

Radhika Rajagopalan Ph.D.

DATE COMPLETED:

9/3/98

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9/10/98