

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Chemistry Review(s)

DEC 27 2000

Division of Dermatological and Dental Drug Products, HFD-540

DMF: [] Type II

Title: Doxycycline Hyclate

1. CHEM REVIEW No. 1

2. REVIEW DATE: 12-Dec-00

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN: Doxycycline hyclate
 Ingredient Dictionary Name: Doxycycline hydrochloride hemihydrate hemioctanolate.
 Tradename: PerioStat
 Manufacturer's Code: MA51
 Chemical Name: [4S-(4α,4aα,5α,5aα,6α,12α)]-4-(Dimethylamino)-,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12-12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenicarboxamide monohydrate.
 CAS Number: 24390-14-5

B. LOCATION IN DMF

| <u>Type of Submission</u> | <u>Date of Submission</u> | <u>Location of Information</u> |
|---------------------------|---------------------------|--------------------------------|
| DMF Amendment | 18-Feb-00 | Vol.6.1, dated 2/18/00 |
| DMF Amendment | 02-Jun-99 | Vol.6.1, dated 6/2/99 |

4. PREVIOUS DOCUMENTS

| <u>Type of Document</u> | <u>Date of Document</u> | <u>Comment</u> |
|-------------------------|-------------------------|-----------------|
| AADA 62-839 / S-008 | 08-Aug-96 | Adequate Review |

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
 ADDRESS:

REPRESENTATIVE or U.S. AGENT (if applicable):

NAME:
 ADDRESS:

6. DMF REFERENCED FOR:

NDA/ANDA/SUPPLEMENT/IND: NDA 50-783
 PRIMARY DMF (as needed):
 APPLICANT NAME: CollaGenex Pharmaceuticals
 LOA DATE: 06-Mar-00
 DRUG PRODUCT NAME: PerioStat
 DOSAGE FORM: Tablet CODE: 500
 STRENGTH: 20 mg
 ROUTE OF ADMINISTRATION: Oral CODE: 001

- 7. **SUPPORTING DOCUMENTS:** AADA 62-839/S-008, Dtd. 8/8/96
- 8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: 14-Jul-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE BEEN PROVIDED: 07-Jul-00
- 10. **CONSULTS:** Not Applicable

11. **COMMENTS:**
The 6/2/99 & 2/18/00 amendments were reviewed. The former amendment referenced a quality system related to doxycycline hyclate manufacturing. The latter reviewed [redacted] as an additional supplier of [redacted]. Both amendments were adequate, however, the latter has an IR.

12. **CONCLUSIONS:**
This review of DMF [redacted] found both the 6/2/99 and 2/18/00 amendments to be ADEQUATE.

However, there is an Informational Request in the 2/18/00 amendment for comparative physical studies to be conducted on the doxycycline hyclate synthesized by each of the [redacted] and [redacted].

[redacted] JS 12/13/00
James D. Vidra, Ph.D.
Review Chemist
HFD-830/HFD-540

[redacted] JS 2/27/00
Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
HFD-830/HFD-540

cc:
DMF [redacted] (2copies)
HFD-540/Div File NDA 50-783
HFD-540/ProjMgr/Cross
HFD-540/ChmTL/DeCamp
R/D Init by JD Vidra

File: Dm [redacted]

Redacted 17

pages of trade

secret and/or

confidential

commercial

information

JAN 10 2001

Division of Dermatological and Dental Drug Products, HFD-540

DMF Number [redacted] **DMF Type II:**
Title: [redacted] **Amendment 90**

1. CHEM REVIEW No. 56

2. REVIEW DATE: January 4, 2001

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN: Not Applicable
Ingredient Dictionary Name: Not Applicable
Tradename: [redacted]
Manufacturer's Code: [redacted]
Chemical Name: Not Applicable
CAS Number: Not Applicable

B. LOCATION IN DMF

| <u>Type of Submission</u> | <u>Date of Submission</u> | <u>Location of Information</u> |
|---------------------------|---------------------------|--------------------------------|
| Amendment 90 | 17-Apr-00 | Vol. 6.1 |
| Amendment 90 | 07-Dec-99 | Vol. 5.1 |

4. PREVIOUS DOCUMENTS

| <u>Type of Document</u> | <u>Date of Document</u> | <u>Comment</u> |
|-------------------------|-------------------------|----------------|
| | | |

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS: [redacted]

CONTACT PERSON'S NAME:
TITLE, DEPARTMENT:
ADDRESS: Same as above.
TELEPHONE: [redacted]

6. DMF REFERENCED FOR:

NDA/ANDA/IND: NDA 50-783
PRIMARY DMF (as needed): Not Applicable
APPLICANT NAME: CollaGenex Pharmaceuticals
LOA DATE: March 7, 2000
DRUG PRODUCT NAME: PerioStat
DOSAGE FORM: Tablet CODE: 500
STRENGTH: 20 mg
ROUTE OF ADMINISTRATION: Oral CODE: 001

7. SUPPORTING DOCUMENTS:

Amendment 22-Feb-00 Update of Authorized Companies

8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: 22-Dec-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE
BEEN PROVIDED: 22-Feb-00
9. **CONSULTS:** Not Applicable
10. **COMMENTS:**
Two Amendment 90s on [redacted] were reviewed and found ADEQUATE.
11. **CONCLUSIONS:** ADEQUATE.

[redacted] /S/ [redacted] 1/4/01

James D. Vidra, Ph.D.

Review Chemist, HFD-830/HFD-540

[redacted] /S/ [redacted] 1/12/01

Wilson H. DeCamp, Ph.D.

Chemistry Team Leader, HFD 830/HFD-540

Attachments (3)

cc:

DMF [redacted] (2 copies)
HFD-540/Division File for NDA 50-783/000
HFD-540/Chm/Vidra
HFD-540/PM/Cross
HFD-540/ChmTL/DeCamp
R/D Init by: Vidra
File: DMF [redacted]

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

Division of Dermatological and Dental Drug Products, HFD-540

DMF: [redacted] DMF Type: III

Title: [redacted]

1. CHEM REVIEW No. 5

2. REVIEW DATE: 08-Jan-01

3. ITEM REVIEWED:

A. IDENTIFICATION

| | |
|-----------------------------|----------------|
| USAN: | Not Applicable |
| Ingredient Dictionary Name: | Not Applicable |
| Tradename: | [redacted] |
| Manufacturer's Code: | [redacted] |
| Chemical Name: | Not Applicable |
| CAS Number: | Not Applicable |

B. LOCATION IN DMF

| <u>Type of Submission</u> | <u>Date of Submission</u> | <u>Location of Information</u> |
|---------------------------|---------------------------|--------------------------------|
| Amendment | 21-Jan-00 | Vols. 2.1 - 2.4 |

4. PREVIOUS DOCUMENTS

| <u>Type of Document</u> | <u>Date of Document</u> | <u>Comment</u> |
|-------------------------|-------------------------|-------------------------|
| Review | 13-Apr-00 | Adequate for [redacted] |
| Review | 26-Apr-00 | Adequate for [redacted] |

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

CONTACT PERSON'S NAME:
ADDRESS:
TELEPHONE:

Same as above.

6. DMF REFERENCED FOR:

NDA/ANDA/SUPPLEMENT/IND: NDA 50-783/000

PRIMARY DMF (as needed): Not Applicable

APPLICANT NAME: CollaGenex Pharmaceuticals, Inc.

LOA DATE: February 14, 2000

DRUG PRODUCT NAME: PerioStat

DOSAGE FORM: Tablet CODE: 500

STRENGTH: 20 mg

ROUTE OF ADMINISTRATION: Oral CODE: 001

7. **SUPPORTING DOCUMENTS:** None
8. **CURRENT STATUS OF DMF:**
DATE OF LAST UPDATE OF DMF: January 21, 2000
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE
BEEN PROVIDED: January 21, 2000
9. **CONSULTS:** Not Applicable
10. **COMMENTS:** ADEQUATE for [redacted]
[redacted]
11. **CONCLUSIONS:** ADEQUATE

[Signature] 1/10/01
James D. Vidra, Ph.D.
Review Chemist, HFD-540/HFD-830

[Signature] 1/10/01
Wilson H. DeCamp, Ph.D.
Review Chemist, HFD-540/HFD-830

Attachments (3)

Cc: DMF [redacted] (2 copies)
HFD-540/DivFile NDA 50-783
HFD-540/PrjMgt/Cross
HFD-540/Chm/Vidra
HFD-540/ChmTL/DeCamp

Redacted 9

pages of trade

secret and/or

confidential

commercial

information

DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-783/000 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 12-Jan-01

| <u>SUBMISSION/TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
|-------------------------------|-----------------------------|-------------------------|-----------------------------|
| Original | 31-Mar-00 | 04-Apr-00 | 10-Apr-00 |
| Amendment BC | 17-Apr-00 | 18-Apr-00 | 02-May-00 |
| Amendment XR | 20-Apr-00 | 21-Apr-00 | NAI on 09-May-00 |
| Amendment BC | 24-Apr-00 | 25-Apr-00 | 01-May-00 |
| Amendment BC | 11-Oct-00 | 12-Oct-00 | 18-Oct-00 |
| Amendment BC | 19-Dec-00 | 20-Dec-00 | 29-Dec-00 |
| Amendment BC | 05-Jan-01 | 09-Jan-01 | 09-Jan-01 |
| Amendment BC | 10-Jan-01 | 11-Jan-01 | 11-Jan-01 |

NAME & ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Senior Director
Drug Development &
Regulatory Affairs
Telephone No. (215) 579-7388
Fax No. (215) 579-8577

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Names/ #'s:

Chemical Type/

Therapeutic Classes:

PerioStat
Doxycycline Hyclate
Doxycycline Hydrochloride
Hemihydrate hemeiethanolate
Antibiotic
3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of Adult Periodontitis

DOSAGE FORM:

Tablet

STRENGTHS:

20 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

Rx X OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL.WT:

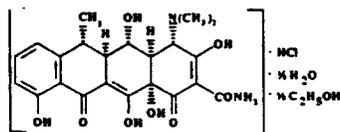
4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacencarboxamide monohydrochloride with ethyl alcohol (2:1) monohydrate.

Molecular Weight:

1025.89

Molecular Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_5OH \cdot 1/2H_2O$

Structural Formula:



doxycycline hyclate

SUPPORTING DOCUMENTS:

| Type / Number | Subject | Holder | Status | Review Date | Letter Date |
|----------------------------|--------------------|----------------------------------|---------------|-------------------------------|--|
| Type II DMF [redacted] | [redacted] | [redacted] | Adequate | 1/3/01 | 3/6/00 |
| Type III DMF [redacted] | | | Adequate | 4/20/00 | 2/22/00 |
| Type III DMF [redacted] | | | Adequate | 1/4/01 | 3/7/00 |
| Type III DMF [redacted] | | | Adequate | 12/19/00 | 3/17/00 |
| Type III DMF [redacted] | | | Both Adequate | o 1g, 4/13/00 o 3g, 1/8/01 | o 1g LOA on 2/14/00 o 3g LOA on 2/14/00 |
| Type III DMF [redacted] | | | Adequate | 9/21/99 | 3/21/00 |
| Type IV DMF [redacted] | | | Adequate | 2/28/00 | 8/23/00 |
| NDA 50-744 | PerioStat Capsules | CollaGenex Pharmaceuticals, Inc. | Approved | 9/30/98 | NA |

REMARKS/COMMENTS:

The PerioStat Tablet is similar to the previously approved PerioStat Capsules (NDA 50-744 approved on 9/30/98) with respect to drug substance concentration and labeling. The clinical indication also remains the same, e.g., for the treatment of adult periodontitis. No additional clinical studies were conducted with the PerioStat Tablets, only bioequivalence studies to demonstrate equivalence with the previous PerioStat Capsules. Most of the tablet ingredients are similar to the capsule ingredients with the exception of the tablet film coating, [redacted] which was reviewed in Type IV DMF [redacted] and found adequate. The major CMC factors to be reviewed in NDA 50-783 include the tablet film coating, the dissolution rate of the tablet (primarily a biopharmaceutical function), the length of stability data for the new drug product, additional product quality tests and the new container closure systems.

PerioStat (doxycycline hyclate) Tablet, 20 mg

The PerioStat Tablets will be sampled in a [redacted] Blister Card of eight tablets and commercialized in 120 cc white [redacted] square bottles containing 60 tablets and in 325 cc [redacted] bottles containing 1,000 tablets. Each of the two bottle also contains a desiccant, [redacted] and a child-resistant white plastic cap with liner.

The drug substance, doxycycline hyclate, was upgraded into a new DMF format from its previous AADA format involving many minor areas. A new supplier, [redacted] was identified that manufactured [redacted] is one of two possible starting materials used in the synthesis of doxycycline hyclate. Drug Master File # [redacted] was found adequate for these drug substance changes.

The two manufacturers and packager were prepared for inspection and found acceptable.

CONCLUSIONS & RECOMMENDATIONS:
NDA 50-783/000 is Recommended for Approval.

/s/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA# 50-783
HFD-540/Division File
HFD-540/DO/Kelsey
HFD-540/PharmTox/See
HFD-540/ProjMan/Cross
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp

filename: N50783.000

Redacted 29

pages of trade

secret and/or

confidential

commercial

information