CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-805

CHEMISTRY REVIEW(S)

NDA 50-805

Oracea (Doxycycline), capsules 40mg
CollaGenex Pharmaceuticals, Inc.

Division of Dermatology and Dental Products

Zhengfang Ge, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA # 50-805

2. REVIEW # 1

3. REVIEW DATE: May 25, 2006

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	August 1, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	COLLAGENEX PHARMACEUTICALS, INC
Address:	41 University Drive, Suite 200, Newtown, PA 18940
Representative:	
Telephone:	215-579-7388

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Oracea
b) Non-Proprietary Name (USAN): Doxycycline
c) CAS No: 17086-28-1
d) Code Name/# (ONDQA only): COL101, MA64
e) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: ~~——~~ inflammatory lesions in patients with rosacea

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 40 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

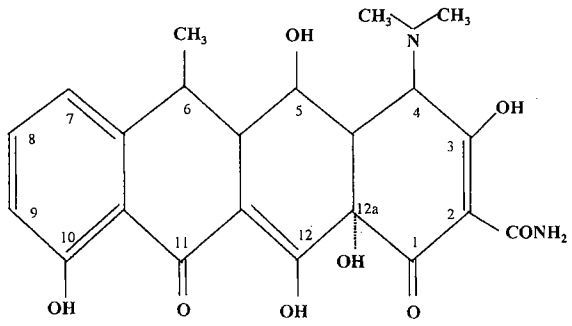
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:

2-Naphthacencecarboxamide, 4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6,methyl-1,11-dioxo-, [4S-(4α, 4aα, 5α, 5aα, 6α,12aα)]-, monohydrate

Molecular Formula: $C_{22}H_{24}N_2O_8 \cdot H_2O$



$.H_2O$

Molecular Weight: 462.46

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					Adequate	1-Sep- 2005	Reviewed for ANDA 65-285, Deoxycycline tablets
					Adequate	3-Apr-2006	Reviewed for this NDA
					Adequate	30-Dec-2002 and 11-June-2003	Dr. George Lunn and Dr. Art Shaw
					Adequate	23-Sep-2005	Dr. D. Klein for NDA
					Adequate	27-Jul-2004	Dr. S. Pope for NDA

		Corp					21-633
[redacted]					Adequate	02-Sep-2003	Dr. B. Wu for ANDA 65-061
					Adequate	07-Jul-2005	Dr. R. Frankewich for NDA 21-882
					N/A		DMF is not available. Since it is a blister component for oral solid dosage form, no DMF review is conducted based on the policy
					Adequate	3-May-2006	Zhengfang Ge, Reviewed for this NDA
					Adequate	19-Sep-2002	Dr. G. Kang Reviewed for ANDA 75-588

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP-2 meeting minutes	IND 67,833	3-May-2004
Amendment (N000BC)	NDA50,805	10-Feb-2006
Amendment (N000C)	NDA50,805	17-Apr-2006
Amendment	NDA50,805	15-May-2006
Amendment	NDA50,805	16-May-2006

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	9-Feb-2006	EER report attached in section IV of this review
Pharm/Tox	Not Applicable		
Biopharm	Acceptable, see review for dissolution	16-May-2006	Dr. Abi Adebowale
LNC	Not Applicable		
Methods Validation	To be submitted post approval		
DMETS	See review notes for labeling comments	15-Mar-2006	Kristina Arnwine
EA	See review notes		
Microbiology	Not applicable		

The Chemistry Review for NDA 50-805

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the CMC review and agreement on the labeling between the sponsor and the Agency, this NDA may be approved. A final review for the labeling mock-up based on the agreement of the labeling modification will be performed and added as an addendum to this review.

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is doxycycline, USP. Doxycycline has 6 chiral centers with a molecular formula $C_{22}H_{24}N_2O_8 \cdot H_2O$ and the molecular weight 462.46. Doxycycline appears in light yellow to pale yellow crystalline powder. It is slightly soluble in water. The pH value for doxycycline (1% w/v suspension in water) is ——— The manufacturer c

The drug product contains two types of doxycycline beads that together provide a dose equivalent to 40 mg of anhydrous doxycycline. The two types of doxycycline beads are 75% immediate-release (IR) beads and 25% delayed-release (DR) beads. The DR beads are made of IR beads coated with a ——— The IR and DR beads are filled into a beige hard gelatin capsule shell. The drug product is packaged ir ——— le with 100 capsules and 30 capsules, and in blister packages for physician samples. The sponsor is marketing the drug product for the bottle of 30 capsules.

The sponsor briefly summarized pharmaceutical development in this section. The development of this drug product is based on Periostat®, an approved immediate release dosage form. The critical steps of the manufacturing process include

Process control data from three primary registration batches are provided in the executed product batch records. Specifications for intermediates (IR and DR beads), and drug products are provided. The drug product specification include appearance, identification, assay, content uniformity, loss on dry and dissolution. The dissolution specification and at 2 hours and 4 hours) originally proposed by the sponsor is too broad at 2 hours based on the test results and dissolution profiles. The sponsor agreed to revise the dissolution specification to and at 2 hours and % at 4 hrs.

The sponsor provided 18 month stability data under 30°C/65%RH and 6 month stability data under 40°C/75%RH for drug products packaged in bottles of 30 capsules and 100 capsules. The sponsor also provided 12 month stability data under 30°C/65%RH and 6 month stability data under 40°C/75%RH for the drug products packaged in blister. Based on the current stability results, 24 months expiration date of the bottled drug products and 18 month expiration date for the blister packaged drug product are recommended. The recommendation of the expiration for the drug products was accepted by the sponsor.

The sponsor proposed to use "doxycycline for the established name. However, doxycycline, USP which already includes should be used in the established name. The sponsor also proposed to use " capsules" for the dosage form. However, the PK profile of the drug product is similar to the commercially available immediate-release capsules, therefore, the should not be used. After several teleconferences with the sponsor, the sponsor agreed to remove " " and " from the labeling. A line of "30 mg immediate-release beads and 10mg delayed-release beads" will be added following the line of dose strength.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for the treatment of the papule and pustule component of rosacea in adult patients.

The drug product (beige opaque capsule printed with CGPI 40) contains doxycycline, USP in an amount equivalent to 40 mg of anhydrous doxycycline. One capsule (40mg) should be administered once daily in the morning on an empty stomach, preferably at least one hour prior to or two hours after meals.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor addressed CMC issues in the NDA submission and amendments for the drug substance and drug product including components/composition, manufacturing process and process control, specifications and stability data. Pre-approval inspection concluded that all manufacturing, testing and packaging facilities were acceptable. After several teleconferences with the sponsor, the

sponsor and the agency agreed on removing ' [redacted] ' and ' [redacted] from the labeling. A line of "30 mg immediate-release beads and 10mg delayed-release beads" will be added following the line of dose strength. From the CMC point of view, this NDA can be approved. The final labeling mock-up based on the agreement between the sponsor and the Agency will be reviewed in an addendum to this review.

III. Administrative

A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee
ProjectManager: Shalini Jain

C. CC Block

44 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1a