

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**50-805**

**MICROBIOLOGY REVIEW**

Oracea  
Clinical Microbiology Review

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY  
PRODUCTS (DAIOP)  
CLINICAL MICROBIOLOGY REVIEW  
CONSULTATION FOR HFD 540**

NDA 50-805

Date Review Completed: May 15, 2006

Date Company Submitted: 29 July 2005  
Date Received (HFD520): 3 August 2005  
Date Assigned: 10 August 2005  
Date Completed: 13 January 2006  
Reviewer: Connie R. Mahon, MS & Avery Goodwin, Ph.D.

**NAME AND ADDRESS OF APPLICANT:**

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**CONTACT PERSON:**

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Vice President, Drug Development & Regulatory Affairs

**DRUG PRODUCT NAME:**

Established Name: Doxycycline — capsules  
Proposed Name for drug product: Oracea™  
Product Code: COL-101  
Chemical Name: alpha-6-deoxy-5-oxytetracycline  
Chemical formula:  $C_{22}H_{24}N_2O_8 \cdot H_2O$   
Molecular Weight: 462.46

**PROPOSED INDICATION:**

To — inflammatory lesions in patients with rosacea

**PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF  
ADMINISTRATION:**

40 mg oral — capsule taken once daily.

**DURATION OF TREATMENT:**

Duration of treatment: 16 weeks

**TYPE OF SUBMISSION:**

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Microbiology Review Consult for HFD 540

**RELATED SUBMISSION:**

IND 67,833 S/021

**PURPOSE OF SUBMISSION:**

The Applicant, Collagenex Pharmaceuticals, Inc. submits an original new drug application (NDA 50-805) for Oracea™ for oral administration to — inflammatory lesions in patients with rosacea. Oracea™ is doxycycline —, which is synthetically derived from oxytetracycline. The dosage form is 40 mg — capsule. Oracea™ is to be taken once daily in the morning.

The Division of Dermatologic and Dental Drug Products has requested a review and assessment of the proposed clinical microbiology subsection of the package insert.

**SUMMARY AND RECOMMENDATIONS**

Collagenex Pharmaceutical has submitted a new drug application (NDA 50-805) for Oracea™ for oral administration to — inflammatory lesions in patients with rosacea. Oracea™ is doxycycline — which is synthetically derived from oxytetracycline. The dosage form is 40 mg — capsule.

From the clinical microbiology perspective, this NDA submission may be approved provided that the Applicant makes the appropriate changes to the microbiology section of the proposed label recommended by the Agency.

The Microbiology Reviewer provides the following changes regarding the Microbiology section of the label for Oracea™:

**AGENCY PROPOSED MICROBIOLOGY SECTION OF THE LABEL**

**MICROBIOLOGY**

*Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with this product during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) is less than the concentration required to treat bacterial diseases. In vivo microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.*

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*TRADENAME should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.*

Under precautions it is suggested that the following be added:

*Bacterial resistance to the tetracyclines may develop in patients using TRADE NAME;*

*Because of the potential for tetracycline-resistant bacteria to develop during the use of TRADE NAME, it should be used only as indicated.*

**BACKGROUND INFORMATION**

Collagenex Pharmaceutical submits a new drug application that references NDA 50-744 for Periostat (doxycycline hyclate) 20 mg capsules and NDA 50-783 for Periostat 20 mg tablets to demonstrate that doxycycline hyclate does not induce recognizable effect on the composition of the gingival flora or result in an increase in antibiotic resistance.

The Applicant proposes the name Oracea for the drug product (doxycycline capsules). Doxycycline is synthetically derived from oxytetracycline. The proposed indication is to inflammatory lesions in patients with rosacea.

Doxycycline is the International non-proprietary name (INN), US Adopted Name (USAN), and the British Approved Name (BAN) for the drug substance used in Oracea™ doxycycline 40 mg capsule. The capsule consists of instantaneous-release (IR) beads containing a total of 30 mg doxycycline and controlled release (CR) beads containing a total of 10 mg. The beads are filled into a hard gelatin capsule shell. (Section 2.7.2.4.1 page 194 NDA 50-805).

With regard to clinical microbiology, the Applicant intends to use cross-study reports from previously submitted NDAs. The Applicant submits two microbiology studies that have assessed the effects of doxycycline hyclate 20 mg BID dose regimen on microflora of the skin for review.

The Sponsor plans to cross-reference previous studies that evaluated Periostat (doxycycline hyclate) 20 mg BID and demonstrated that a 9-18 month regimen of Periostat did not exert a discernable effect on the composition of the subgingival flora or result in an increase in antibiotic resistance. The three microbiology studies to be cited by reference to NDA 50-744 include:

- Study 5732.11A: A 3 month, randomized, placebo-controlled clinical study to

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evaluate the microbial effects of five dose regimens of doxycycline hyclate on the oral cavity

- Study 5732.11 E&F: A 12 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects of 10 mg QD, 20 mg QD, and 20 mg BID of doxycycline hyclate on the oral cavity
- Study 5732.11 H: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects 20 mg BID of doxycycline hyclate on the oral cavity

For the COL- 101 NDA, the Sponsor plans to submit two microbiology studies for review:

- Study 5732.11 J: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects 20 mg BID of doxycycline hyclate on the intestinal and vaginal flora
- Study DERM-301: A 6 month, randomized, double-blind, placebo-controlled study to determine the microbial effects 20 mg bid of doxycycline hyclate on the skin microflora

In the draft product labeling, the Sponsor proposes the following in the microbiology subsection and asks if the Agency agrees.

*“Microbiology: Doxycycline is a member of the tetracycline class of antibiotics. The plasma concentration of doxycycline achieved with this product during administration is*

[ ]

The Sponsor also proposes to include the following statements regarding the mechanism of action:

[ ]

INTRODUCTION

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ROSACEA

Rosacea is a chronic condition characterized by transient or persistent central facial erythema, visible blood vessels, and often papules and pustules. The principal subtypes of rosacea include erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea<sup>1</sup>. Rosacea is a disease for which there is no laboratory benchmark test. Therefore, the diagnosis of rosacea is a clinical one; defined by recognizable morphologic characteristics (vascular in origin) which may lead to difficulties in interpretation. Despite an incomplete understanding of the pathogenesis of rosacea, therapeutic modality continues to expand. However, the exact causes of these manifestations are unknown.

Rosacea usually occurs between the ages of 30 and 50 years and the disease is accompanied by chronic episodes with remissions and relapses<sup>2</sup>. The prevalence of rosacea was reported to be 14% in women and 5% in men. Exacerbating factors such as heat, alcohol, stress, certain medications, certain foods and sunlight has been identified by some individuals<sup>3</sup>. Rosacea has also been anecdotally reported to be associated with *Helicobacter pylori*<sup>4</sup> and Demodex<sup>5</sup>, a common inhabitant of the normal human skin.

Published studies have addressed the possible role of *H. pylori* as a causative agent for rosacea. However, there is no statistically significant association between infection and acne rosacea. A study by Argenziano *et al.*<sup>6</sup> evaluated patients with acne rosacea and found anti- *H. pylori* IgG antibodies in 81% of the acne rosacea patients with dyspepsia and 16% of those without dyspeptic symptoms. Anti-CagA IgG, a marker for *H. pylori* infection, was found in 75% of the dyspeptic patients but in none of those without gastric symptoms. A correlation was proposed between the severity of rosacea and the presence of these antibodies, but the subgroup included only 18 patients and no statistical analysis was provided.

The mite *Demodex folliculorum*, part of the skin's normal flora, has also been examined as a potential contributing factor to rosacea, but study results have been inconclusive<sup>5</sup>. The mite *Demodex* spp., belonging to the Class Arachnida, Order Acarina, lives around hair follicles (*Demodex folliculorum hominis*) or in the secretory ducts of sebaceous (fat) glands connected to the hair follicles (*Demodex brevis*) of humans. The preferred sites are facial skin, forehead, cheeks, eyelashes and external ear channels. The size of demodices varies from 0.1 mm to 0.4 mm. Adult parasites have four pairs of short legs. They can slowly move on the skin especially during the night. In humans, the infestation is known as 'demodicosis' and occurs world-wide. The tendency for the clinical manifestations of rosacea to appear later in life parallels the increase *Demodex* mite density that occurs with age<sup>7</sup>. The infestation may be frequently free of symptoms. Inflammation in acute and chronic forms may occur due to demodicosis in humans. Therapeutic agents that may

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be active against the organism include metronidazole, sulfur preparations, sulfacetamide sodium, and tetracycline<sup>7</sup>.

**MICROBIOLOGY STUDIES**

**Study DERM 301**

DERM 301 was a 6 month, randomized, double-blind placebo controlled study to determine the microbial effects of 20 mg BID of doxycycline hyclate on the skin microflora. The twice daily dosage at 20 mg was chosen since it resulted in a mean maximum and average steady-state plasma concentration of 0.79 µg/ml and 0.48 µg/ml respectively, after 1.5 hours. The study DERM 310 attempted to assess if treatment with subantimicrobial-dose (SD) doxycycline (20 mg tablets twice daily) improved clinical outcome but led to overgrowth or colonization of skin by opportunistic pathogens or resulted in an increase in antibiotic resistance by the surface skin microflora in patients with moderate acne compared with placebo.

The study involved 51(N) adults with moderate facial acne. The patients were randomized to receive SD doxycycline or placebo twice daily for 6 months. The primary efficacy outcome measure was changes from baseline in numbers of inflammatory, non-inflammatory, and total lesions. Secondary efficacy outcome was changes from baseline of individual counts of papules, pustules and modules, and global assessments of clinical improvement by patient and physician.

The microbiological objectives of the study were to determine whether twice daily SD doxycycline therapy 1) had any detectable antimicrobial effect on the normal flora 2) led to overgrowth or colonization of the skin by opportunistic pathogens 3) resulted in an increase in resistance in the predominant skin microflora.

**Microbiology Procedures**

The microbiology objectives of the study were to determine whether twice-daily doxycycline therapy had any detectable antimicrobial effect on the normal skin flora that led to overgrowth or colonization of the skin by opportunistic pathogens; or resulted in an increase in antibiotic resistance in the predominant skin microflora. Microbial samples of the surface of the skin were collected from a 2 cm<sup>2</sup> area in the center of the brow at baseline and after six (6) months of treatment. The sample was collected by placing a 2 cm<sup>2</sup> template, and gently rubbing a sterile cotton swab over the area. The swab was placed in a tube containing 1.0 mL of pre-reduced, anaerobically-sterilized Ringer solution and immediately transported to the laboratory for processing.

Samples were plated on non-selective media to determine the total number of anaerobic

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and facultative organisms were determined from the plate dilutions that gave rise to 30 to 300 colony forming units (CFUs). The fewer than 30 colonies on the most diluted plate, the actual number of colonies was counted.

Doxycycline-resistant bacteria were detected by placing the sample on non-selective medium containing 4 µg/mL of doxycycline. The number of anaerobic bacteria and facultative bacteria resistant to at least 4 µg of doxycycline were determined and expressed as percentage of the total for each organism. Isolates were identified by genus and species whenever possible. Isolates were tested for susceptibility to determine the MIC required to inhibit visible growth on the agar medium. The MIC<sub>50</sub> and MIC<sub>90</sub> were calculated for all bacterial organisms for each group at each sample period. Susceptibility testing was performed on media containing doxycycline, minocycline, tetracycline, erythromycin, clindamycin, and vancomycin by agar dilution method.

Microbiological data were analyzed using the unpaired t test. If the data did not follow a normal distribution, the non-parametric Mann-Whitney test was used to avoid bias of outliers. Differences within groups were evaluated using a paired t test or rank sum test.

Microbiology Findings

The results of the study indicate that the differences in microbial colony counts between or within the groups from baseline were not statistically significant. These findings appear to also indicate that no significant change in the composition of the normal skin flora was observed.

Additionally, the report also indicated that antibiotic susceptibility testing showed no differences between or within the study groups in the MICs obtained from doxycycline. The report also indicated that there were no strong correlations between resistance to doxycycline and resistance to any of the five (5) other antibiotics tested. However, moderate correlations ( $r=0.5$ ) were detected between doxycycline and both tetracycline and minocycline. Bacteria resistant to one tetracycline class are often resistant to others; therefore, cross-resistance between doxycycline and other tetracyclines was not unexpected. No differences between the correlation coefficients for cross-resistance in the doxycycline 6-month samples and either placebo 6 month samples or the doxycycline baseline samples were observed.

Conclusions

In Study DERM-301, the Applicant reports that a 6-month regimen of 20 mg BID resulted in 1) no effect on the cultivable microflora of the skin; 2) no emergence of resistant microorganisms; and 3) no development of multi-antibiotic resistance, including Vancomycin.

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The results presented in the report provided by the Applicant indicated that treatment with SD doxycycline twice daily had no effect on skin microflora including *Propionibacterium acnes*. There was also no observed change in the composition of the normal skin flora. The report indicated that the treatment did not result in the emergence of organisms resistant to doxycycline or cross-resistance to other antimicrobial agents. Increase in the proportion of flora resistant to doxycycline or increase in MIC values for bacteria resistant to 4 µg/mL of doxycycline was not observed. Evidence of development of cross-resistance between doxycycline and related or un-related antibiotics was not reported.

**Study 5732.11 J**

A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects 20 mg BID of doxycycline hyclate on the intestinal and vaginal flora

The purpose of this study was to determine if a nine-month regimen of sub-antimicrobial doxycycline dose (SDD) of 20 mg b.i.d. had an effect on either the intestinal or the vaginal microflora. Sixty-nine (69) periodontal diseased subjects (30-75 years of age) were randomized to receive drug or placebo control for a 9 month period. Stool samples and vaginal swabs were collected at baseline and after three (3) and 9 months of therapy. Samples were examined for total anaerobic counts, opportunistic pathogens and doxycycline-resistant ( $\geq 4$  µg/mL) bacteria. All recovered isolates were identified and susceptibility tests to five additional antimicrobials were determined.

**Microbiology Procedures**

*Fecal Samples*

Fecal sample collection kits that included all materials needed to collect the sample and written instructions for collection and handling were provided for each subject. Once received at the clinical site, samples were shipped to the microbiology testing laboratory. Samples were weighed, placed into anaerobically-sterilized, pre-reduced (PRAS) Ringers solution. The samples were sonicated briefly to disperse the organisms and then serial 10-fold dilutions were made in Ringers solution. The samples were placed in culture media appropriate for the target microorganisms and incubated in the incubation conditions required by the target organisms.

Cultures were examined for growth following the indicated incubation period. Colony-forming units (CFUs) of anaerobic and aerobic organisms were determined from the plate dilution that gave rise to 30-300 CFUs if available. If less than 30 colonies were present on the most diluted plate, the number of colonies were counted, provided that more than a

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Bacteroides	22.97	20.00	15.15	10.00	27.63	32.73
Bifidobacterium	6.76	12.31	19.70	18.00	10.53	3.64
Clostridium	2.70	1.54	4.55	0.00	1.32	5.45
Eubacterium	12.16	13.85	3.03	6.00	2.63	5.45
Fusobacterium	14.86	9.23	6.06	10.00	0.00	3.64
Prevotella	5.41	13.54	6.06	8.00	10.53	7.27
Unidentified Gram negative rods	13.51	10.77	22.73	22.00	23.68	18.18

The median counts,  $\log_{10}$  (wet-weight-adjusted) for sub-therapeutic doxycycline dose (SDD) or placebo treatments in the microbial groups examined from the fecal flora are shown in Table 2.

Table 2: Median  $\log_{10}$  wet-weight-adjusted counts and two-sample median test analysis for differences between SDD and placebo treatments for the fecal flora

Microbial Group	Baseline			3-Month			9-Month		
	SDD	Placebo	p-value	SDD	Placebo	p-value	SDD	Placebo	p-value
Total Anaerobic counts	7.02	6.97	0.7173	7.16	7.03	0.999	7.61	7.59	0.8129
Doxycycline-resistant counts	5.78	5.50	0.0279	7.19	5.80	0.773	6.85	6.63	0.1294
Candida	1.79	2.10	0.999	2.88	3.45	0.6256	2.43	2.23	0.999
Total Enterics	3.81	4.02	0.5963	4.02	3.91	0.8748	3.11	3.83	0.3368
<i>Staphylococcus aureus</i>	2.56	2.43	0.7782	3.38	4.42	0.3173	1.85	2.6	0.2542
Change from baseline	NA	NA	NA	1.71	0.15	0.0927	1.21	1.31	0.8984
Doxycycline-resistant counts				2.99	2.24		1.42	1.42	

Between the two treatment groups, statistically significant difference ( $p < 0.05$ ) was detected in the doxycycline resistant counts present at the baseline sampling period. At this sampling period, prior to the administration of study drug, the CFUs of doxycycline-resistant organisms detected from the SDD treatment group were significantly higher than the placebo control. At the 3 month or the 9 month sample periods, however, there was no between-sample difference in doxycycline-resistant counts detected.

The  $MIC_{50}$ ,  $MIC_{90}$  and range for doxycycline-resistant organisms are shown in Table 3. There were no differences in the values obtained within the SDD treatment groups or between SDD and placebo treatment groups. The values obtained for the doxycycline-resistant bacteria recovered from the SDD group appeared comparable to those of the placebo group.

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Table 3: Susceptibilities to doxycycline ( $\mu\text{g/mL}$ ) of predominant bacteria recovered on medium containing 4  $\mu\text{g/mL}$  doxycycline from each treatment group and sample period.

MICs in $\mu\text{g/mL}$	SDD			Placebo		
	Baseline	3 months	9 months	Baseline	3 months	9 months
MIC <sub>50</sub>	16	32	16	16	32	8
MIC <sub>90</sub>	32	>32	32	32	>32	>32
Range	0.06->32	0.06->32	0.25->32	0.06->32	0.06->32	0.25->32

MICs to doxycycline and 5 other antibiotics were determined for all isolates recovered from doxycycline-containing culture media. The data were analyzed to show changes in the resistance of these organisms. Correlation coefficients values were calculated between the MICs obtained for doxycycline and the 5 other antibiotics tested against predominant organisms recovered on medium containing 4  $\mu\text{g}$  of doxycycline per ml. Table 4 shows the result of the correlation coefficient analysis. The data indicate that there was no consistently strong correlation between doxycycline and any of the three non-tetracycline antibiotic tested. However, a strong correlation between doxycycline and minocycline, and doxycycline and tetracycline was observed.

Table 4: Correlations between MICs obtained for doxycycline with each of the other 5 antimicrobials tested against predominant bacteria recovered from medium containing 4  $\mu\text{g/mL}$  doxycycline at each sample period fro each treatment.

Sample Period and Treatment Group	Minocycline	Tetracycline	Amoxicillin	Erythromycin	Clindamycin
Baseline SDD	0.497	0.589	0.178	0.283	0.272
Baseline Placebo	0.546	0.495	0.268	0.474	0.335
3 month SDD	0.616	0.592	0.099	0.124	0.420
3 month Placebo	0.618	0.653	0.083	0.195	0.628
9 month SDD	0.683	0.364	0.266	0.415	0.114
9 month Placebo	0.500	0.393	0.069	0.510	0.435

These results indicate that treatment with SDD does not tend to promote a greater chance for the development of cross-resistance with any of the non-tetracycline antibiotics tested. However, as can be expected, because of the close molecular and pharmacodynamic similarities between doxycycline and minocycline and doxycycline and tetracycline, it is conceivable that prolonged use of SDD may promote the emergence of resistance to tetracycline and its derivatives.

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*Vaginal Sample Flora Analyses*

The number of vaginal samples received was less than initially projected and was further reduced when several samples failed to produce growth on preliminary culture. The numbers of isolates recovered were too low to allow for any meaningful analysis in regard to the particular bacterial species present. Although the Applicant reported results of the unpaired t-test to analyze the culture counts in an attempt to determine if significant changes occurred between treatments, interpretation of the analysis is difficult. The Applicant reported that the distribution of the data was not normal which could have led to false positives (Type I error), and therefore, the reported p-values  $< 0.050$  should be interpreted with caution. Nevertheless, the Applicant indicated that no apparent statistically significant differences were detected between SDD and placebo treatments at any time.

Conclusions

This investigation made an attempt to determine if SDD exerted any detectable effect on the intestinal flora that could be attributed to antimicrobial activity. The levels of doxycycline used was below the reported MIC, however, at this level, the possibility exist that this concentration may be inhibitory for certain organisms that are ubiquitously sensitive to tetracyclines. Based on the data presented in this study, there appear to be no significant differences between treatment groups in terms of MIC. The levels of doxycycline present in the intestine appeared lower than that required for stimulating any significant change in MIC. There were no observable changes in the MIC<sub>50</sub> or MIC<sub>90</sub> values. Please note that longer treatment duration or results obtained from a larger patient sample may show a trend towards the development of doxycycline resistance. However, such a test was not performed.

The number of vaginal samples obtained was lower than what was initially expected. This was attributed to inadequate sample collection, storage, and transport. Therefore, the samples were not enough to draw any significant conclusion. However, from the limited samples that were available, the data indicate that low dose doxycycline did not appear to have an effect on vaginal candidiasis since yeast was only recovered from one subject. Please note that the clinical data indicated that there were 3 incidences of vaginitis (2 in the SDD group and 1 in the placebo group) over the 9 month course of treatment. However, the significance of this finding is not known.

**SYNOPSIS OF CLINICAL PROTOCOLS: COL 101-ROSE-301 AND COL 101-ROSE 302**

The Applicant conducted two, (COL-101 ROSE-301 and COL-101 ROSE-302), multi-center, randomized, double-blind, placebo-controlled, parallel-group, outpatient, phase 3

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trials to evaluate the safety and efficacy of doxycycline for reducing total inflammatory lesions associated with rosacea. A total of 537 patients (142 COL- 101, 144 placebo patients for ROSE 302 with a total of 286 patients; 127 COL101, 124 placebo patients for ROSE 301 with a total of 251 patients) were included in the study. Patients visited the clinics for evaluations at baseline and at Weeks 3, 6, 12, 16, and 20. Patients were evaluated at each visit for the number and types of lesions, and other assessments including adverse events. The Investigator's Global Assessment (IGA) and the Clinician's Erythema Assessment (CEA) Scale scores were obtained at each visit. Study drug treatment ceased at Week 16 and patients returned for follow-up clinical and safety evaluations at Week 20.

This study did not include any microbiological studies for evaluation. The primary efficacy variable during the double-blind treatment period was change in total inflammatory lesion count (papules + pustules + nodules) from baseline to Week 16. Secondary efficacy parameters included the change from baseline to Week 16 in the CEA scale score, change from baseline to week 16 in the IGA score, and the proportion of treatment responders at Week 16 based on the IGA.

Criteria for evaluation

Maintenance of response after 4 weeks post-treatment was assessed using the following parameters: change in total inflammatory lesion count (papules + pustules + nodules) from Week 16 to Week 20; change from Week 16 to Week 20 in the CEA scale score; change from Week 16 to Week 20 in the IGA score; and the proportion of treatment responders at week 20 based on the IGA. The investigator's global assessment scale is depicted in Table 5.

Table 5: Investigators Global Assessment (IGA) Scale.

Grade	Definition	Guideline
0 Clear	No signs or symptoms present	Skin is completely clear of inflammatory lesions
1 Near clear	One or two papules	1 or 2 small, non-inflammatory papules
2 Mild	Some papules/pustules	3 to 10 papules/pustules
3 Moderate	Moderate number of papules/pustules	11 to 19 papules/pustules
4 Severe	Numerous papules/pustules; nodules	>20 papules/pustules and nodules

Patients with a score of 0 or 1 were categorized as treatment "successes" regardless of their baseline IGA values or baseline lesion counts, and patients who did not meet this criterion were categorized as treatment "failures". The change in the CEA total score

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from baseline to endpoint (Week 16) was also evaluated as secondary efficacy parameter. The clinician used the scale shown below (Table 6) to evaluate five facial areas: forehead, chin, nose, right cheek, and left cheek. The CEA total score was the sum of the scores from the five facial areas.

Table 6: Clinician's Erythema Assessment (CEA) Scale

Grade	Definition
0 None	No redness present
1 Mild	Slight pinkness
2 Moderate	Definite redness
3 Significant	Marked erythema
4 Severe	Fiery redness

**Summary of Efficacy Findings**

The Applicant chose the change in total inflammatory lesion count from baseline to Week 16 (end of treatment) as the sole primary endpoint in these studies. Counts of papules, pustules, and nodules represented a standard and objective measurement for evaluating the effects of a study medication on rosacea, and was the most directly relevant measure to support the proposed indication for Oracea, "to reduce inflammatory lesions in patients with rosacea", according to the Applicant (Section 2.5.4.2 pg 90, NDA 50-805).

The result in Table 7 shows the total inflammatory lesion count for studies 301, 302, and combined studies demonstrating the mean change that occurred from baseline to Week 16. In this table, it shows that in all studies (301, 302, and combined) statistically significant ( $p < 0.001$ ) reduction in total inflammatory count from baseline to Week 16 in patients treated with Oracea compared with placebo treatment groups. From baseline counts of 20 in the Oracea group and 20.8 in the placebo group in the combined analysis, the mean change at Week 16 was -10.6 in the Oracea group versus -5.1 in the placebo group. In Study 301, the mean change was -11.8 in the Oracea group while the placebo group showed -5.9; Study 302, Oracea group shows -9.5 while placebo, -4.3 ( $p < 0.001$ ).

Table 7: Total Inflammatory Lesion Count: Mean Change from Baseline and Week 16 (ITT population).

Visit	Study 301		Study 302		Combined studies	
	Oracea™ (n=127)	Placebo n=124	Oracea™ (n=142)	Placebo (n=144)	Oracea™ (n=169)	Placebo (n=268)
Baseline Mean	19.5	20.3	20.5	21.2	20.0	20.8
Median (range)	17(10-39)	17.0(10-63)	17.0(10-105)	18 (10-100)	17(10-105)	17.5(10-100)
Week 16 <sup>a</sup> Mean	7.7	14.4	11.0	16.9	9.4	15.7
Median (range)	5.0(0-38)	9.0 (0-	8(0-105)	13.0(1-78)	7(0-105)	11.0(0-

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Change from Baseline to Week 16 Mean	-11.8	-5.9	-9.5	-4.3	-10.6	-5.1
Median (range)	-10(-38 to 11)	-8.0 (-46-89)	-8.0 (-41 to 28)	6.0 (-34 to 38)	-9.0(-41 to 28)	-7(-46-89)
p value <sup>b</sup>	<0.001		<0.001		<0.001	

Source: Table 9.1 (NDA 50-805; Module 5, 301- vol 1.9 pp 118; 302- vol 1.32, p 134; combined vol 1.56, p 10)

a: Week 16 was the last valid observation available on treatment.

b: p-value for treatment difference on change from baseline, using a Van Elteren test stratified by pooled center

In the Clinician's Erythema Assessment (CEA) total score, the results of the combined analysis (Table 8) show a significant reduction in the Oracea group than in the placebo group at Week 16, with a change in baseline of -2.0 in the Oracea group versus -1.5 in the placebo group (p=0.024). In study 301, the change from baseline was -2.7 in the Oracea group versus -1.8 in the placebo group (p=0.017) while in Study 302, the change from baseline to Week 16 was -1.4 in the Oracea group and -1.2 in the placebo group (p=0.428). It appears that the effect on erythema is less evident than in the total inflammatory lesion counts.

Table 8: Clinician's Erythema Assessment (CEA) Score: Mean Change from Baseline and Week 16 (ITT population).

Visit	Study 301		Study 302		Combined studies	
	Oracea™ (n=127)	Placebo (n=124)	Oracea™ (n=142)	Placebo (n=144)	Oracea™ (n=169)	Placebo (n=268)
Baseline Mean	9.7	9.5	9.5	9.1	9.6	9.3
Median (range)	9.0(5-19)	9.0(5-19)	9.0 (4-18)	9.0 (4-16)	9.0 (4-19)	9.0 (4-19)
Week 16 <sup>a</sup> Mean	7.0	7.7	8.1	7.9	7.6	7.8
Median (range)	7.0(0-18)	8.0 (0-19)	8(0-18)	8.0(0-19)	8.0 (0-18)	8.0(0-19)
Change from Baseline to Week 16 Mean	-2.7	-1.8	-1.4	-1.2	-2.0	-1.5
Median (range)	-3 (-10 to 5)	-1.0 (-10 to 5)	-1.0 (-10 to 6)	-1.0 (-9 to 9)	-2.0(-10 to 6)	-1.0(-10-9)
p value <sup>b</sup>	0.017		0.428		0.024	

Source: Table 9.1 (NDA 50-805; Module 5, 301- vol 1.9 pp 224; 302- vol 1.32, p 256; combined vol 1.56, p 38)

a: Week 16 was the last valid observation available on treatment.

b: p-value for treatment difference on change from baseline, using an ANOVA model with treatment and pooled center as the main effects

The Applicant also provided results of the Investigator's Global Assessment (IGA) Scores at baseline and the change observed from baseline at Week 16 (Table 9). The table shows that at baseline, the scores were similar between the Oracea and the placebo groups. The results show statistically significant improvement from baseline scores and at Week 16 in Study 301 produced 55/127 (35.4%) for Oracea group and 32/127 (25%) for placebo(p=0.001); Study 302, 32/142(22.5%) for Oracea group and 23/144(16%) in the



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The results provided by the Applicant of each of the individual study and across both the studies combined indicate that the reduction in total inflammatory lesion count in the Oracea group was significantly greater than the placebo group at Week 16 ( $p < 0.001$ ).

For the CEA total score, the ITT results of study 301 and the combined analysis showed a significantly greater reduction in the Oracea group than in the placebo group at Week 16. These results indicate that Oracea has a favorable effect on erythema, although in Study 302, the change from baseline was found for both treatment groups and the difference was not statistically significant.

For the IGA scores, the results indicate that patients in the Oracea group showed greater improvement at Week 16 compared to patients in the placebo group.

**SUMMARY AND RECOMMENDATIONS**

Collagenex Pharmaceutical has submitted a new drug application (NDA 50-805) for Oracea™ for oral administration to ~~the~~ inflammatory lesions in patients with rosacea. Oracea™ is doxycycline ~~hydrochloride~~, which is synthetically derived from oxytetracycline. The dosage form is 40 mg ~~capsule~~.

From the clinical microbiology perspective, this NDA submission may be approved provided that the Applicant makes the appropriate changes to the microbiology section of the proposed label recommended by the Agency.

The Microbiology Reviewer provides the following changes regarding the Microbiology section of the label for Oracea™:

**AGENCY PROPOSED MICROBIOLOGY SECTION OF THE LABEL**

**MICROBIOLOGY**

*Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with this product during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) is less than the concentration required to treat bacterial diseases. In vivo microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.*

*TRADENAME should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.*

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Under precautions it is suggested that the following be added:

*Bacterial resistance to the tetracyclines may develop in patients using TRADE NAME;*

~~\_\_\_\_\_~~  
*Because of the potential for tetracycline-resistant bacteria to develop during the use of TRADE NAME, it should be used only as indicated.*

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