

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-808

MICROBIOLOGY REVIEW

DIVISION OF ANTIINFECTIVE AND OPHTHALMOLOGY PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW
CONSULT FOR DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS (HFD-540)

N50-808 Minocycline ER — Medicis

Date review Completed: 3 Apr 06

Date Company Submitted: 30 June 2005

Date Received (HFD 520): 15 August 2005

Date Assigned: 15 August 2005

Reviewer: Connie R. Mahon, MS (Fred Marsik completed review due to C. Mahon departure from HFD-520)

NAME AND ADDRESS OF APPLICANT

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DRUG PRODUCT NAME

Established Name: Minocycline hydrochloride
Proprietary Name: Solodyn™ (minocycline hydrochloride Modified Release —)
Chemical Name: 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide monohydrochloride
Chemical formula: C₂₃H₂₇N₃O₇·HCL
Molecular Weight: —

PROPOSED INDICATION

Primary treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.

PROPOSED DOSAGE FORM: 45, 90, 135 mg of minocycline hydrochloride . —

DOSAGE, STRENGTH, ROUTE OF ADMINISTRATION: 1 mg/kg/day (0.76-1.50 mg/kg/day), depending on the weight of the patient (29-57 mg/m²/day) Oral

DURATION OF TREATMENT:

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DISPENSED: Rx

RELATED DOCUMENTS REVIEWED: IND 65 398 S0017, IND 65 398 S032

TYPE OF SUBMISSION: Microbiology Review Consultation for the Division of Dermatologic and Dental Products (HFD 540).

PURPOSE OF SUBMISSION: The Applicant, MEDICIS Pharmaceutical Corp, submits an original new drug application (NDA) N 50-808, for a new modified release formulation of minocycline in 45 mg, 90 mg and 135 mg — as a primary therapy in moderate-to severe acne vulgaris. The new modified release formulation includes the identical active pharmaceutical ingredient to currently marketed minocycline, but it includes additional excipients that are necessary in a modified-release formulation. This new formulation is not bioequivalent to the marketed product.

Applicable IND/NDA Minocycline HCl was FDA approved (NDA 05-0451) in 10 August 1984 (Lederle Laboratories). Dynacin® (minocycline HCl) was approved (ANDA 065-131) on 16 April 2003. (N 50-808 Section 2.4.1.5)

The Applicant submits reports of 12 clinical studies and 21 nonclinical studies conducted by Medicis under IND 65,398 to support this application.

The Division of Dermatologic and Dental Drug Products has requested a review and assessment of the proposed Clinical Microbiology subsection of the Clinical Pharmacology section of the proposed draft label (package insert). The Applicant includes in this submission the study report in the evaluation of the antimicrobial effects in vivo of minocycline — in humans (MEDICIS Protocol MP-0104-09).

SUMMARY AND RECOMMENDATIONS

Propionibacterium acnes is a strictly anaerobic gram-positive bacillus that has been associated with acne vulgaris. Microbiology studies performed during the clinical studies attempted to determine the relative antimicrobial effects of the modified-release formulation of minocycline by measuring its inhibitory effects against *P. acnes* in vivo.

The results of the clinical studies performed by the Applicant, met the primary and secondary efficacy evaluation criteria. However, the study to show correlation between *P. acnes* colony counts in culture with severity assessment scores indicated that culture results are independent of the severity of acne assessment scores.

From a microbiology perspective the product is approvable with the following changes to the "Indication" and "Microbiology" sections of the package insert (See Agency's proposed "INDICATION" and "MICROBIOLOGY" sections of package insert below).

2 Page(s) Withheld

 Trade Secret / Confidential

 P Draft Labeling

 Deliberative Process

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BACKGROUND AND INTRODUCTION

Minocycline is an approved prescription drug product originally marketed in the United States under the trade name of Minocin® (Lederle/Wyeth Laboratories). Currently, minocycline is a generic prescription drug product and is marketed as an immediate release formulation by MEDICIS under the brand name of Dynacin®. Minocycline is indicated for a number of antibacterial infections, including use as adjuvant therapy for acne vulgaris (3,4). Minocycline (Dynacin®) is supplied as the hydrochloride in aqueous film coated tablets equivalent to 50, 75, or 100 mg of minocycline.

The recommended adult oral dosage for the immediate release formulation of minocycline (Dynacin®) is 200 mg (3.1 mg/kg or 118 mg/m², based on an individual with an average individual body weight of 65 kg) initially followed by 100 mg every 12 hours (59 mg/m² *bid*) or 50 mg every 4 hours (29 mg/m² *qid*). The recommended pediatric oral dose for the immediate release formulation of minocycline (Dynacin®) is 4 mg/kg (140 mg/m² based on an average individual body weight of 50 kg) initially followed by 2 mg/kg every 12 hours (70 mg/m² *bid*) (Section 2.4.1.2).

MEDICIS Pharmaceutical Corporation proposes a modified-release formulation, Solodyn™, a prescription drug product that contains 45, 90, or 135 mg of minocycline. The intended clinical indication is for the treatment of inflammatory lesions associated with moderate-to-severe *acne vulgaris*. The recommended dose will be 1 mg/kg/day (0.76 – 1.50 mg/kg/day, depending on the weight of the patient, or 29 – 57 mg/m²/day).

Acne vulgaris

Acne vulgaris is an inflammatory skin disorder characterized by the presence of eruptions, predominantly in the face, upper back and chest, made up of comedones, cysts, papules, and pustules on an inflammatory base. The severity of acne can be assessed and ranked into mild, moderate, and severe. In mild disease, open and closed comedones and some papules and pustules are present. Moderate acne consists of more frequent occurrence of papules and pustules with mild scarring while severe disease contains all of the previously mentioned manifestations, and in addition, nodular abscesses and often leads to more extensive scarring (1). Acne vulgaris has a complex etiology that involves abnormal keratinization, hormonal function, bacterial growth and immune hypersensitivity. The disease occurs usually during puberty and adolescence because of androgenic stimulation of sebum secretion, plugging of follicles by keratinization associated with *Propionibacterium acnes* proliferation M (1). The primary acne lesion, “blackhead” is an impaction and distention of the follicle with improperly desquamated keratinocytes and sebum. During puberty, androgens stimulate the production of sebum. Pre-existing comedones, clinically unapparent at the time before the pimple shows, become filled with

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lipid and may enlarge to become visible.

The role of *P. acne acnes* in acne vulgaris has been reported in the literature (2). *P. acnes* is a strict anaerobic gram-positive non-sporeforming bacillus and a member of the normal skin flora. Proliferation of *P. acnes* is considered to be critical for the development of inflammatory lesions. The blocked follicles become an ideal anaerobic culture environment which contains nutrients including lipid substrates. *P. acnes* metabolizes sebaceous triglycerides, consumes the glycerol fraction, and discards free fatty acids. As a consequence, this organism is able to produce neutrophil chemical attractants, activate complement, and in general, stimulate inflammatory response. Although the suppression of *P. acnes* has been associated with clinical improvement, the absolute numbers have not been correlated with the severity of the disease (3,4).

Treatment Regimens for Acne Vulgaris

Historically, anti-acne agents have included topical or systemic antibiotics or application of retinoids. Table 1 shows the typical treatment regimens for acne vulgaris.

Table 1. Typical Treatment Regimens for Acne Vulgaris (3)

Severity of Disease	Treatment Regimen
Comedonal Acne	Topical tretinoin, adapalene, or tazarotene applied daily
	Salicylic acid
	Azalaic acid
Mild Papulopustular acne	Benzoyl peroxide
	Topical gel preparations of benzoyl peroxide with either clindamycin or erythromycin
	Oral doxycycline or minocycline 750/100 mg twice daily plus topical retinoid
Severe Papulopustular or Nodular Acne	Oral doxycycline or minocycline plus topical retinoid
	Isotretinoin 1 mg/kg a day

Topical treatment has been found to be appropriate for most mild papulopustular acne. Usually, an antibacterial and a comedolytic are prescribed. When acne becomes resistant to topical treatment or scarring or nodular lesions appear, then oral antibiotics are often required. Most of the antibiotics used in acne therapy also provide an anti-inflammatory effect in addition to their inhibitory effect on *P. acnes*. The oral antibiotics used routinely in the treatment of acne vulgaris include erythromycin, clindamycin, and tetracyclines. Increase of resistance to erythromycin in *P. acnes* has been widely reported and has reduced its use. Acquired resistance to minocycline and doxycycline is not as common as

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to erythromycin although it remains a major concern. Because of long-term use of antibiotics in acne therapy, considerable selective pressure for the development of resistant *P. acnes* exists. Combined resistance to erythromycin and clindamycin in 20% of follicular propionibacteria isolates from acne patients treated with topical formulations of either drug has been reported in the US as early as the late '70s. Resistance of *P. acnes* to tetracycline has also been reported in the US. A study published by Ross was the first report of high-level resistance to minocycline (4-6 mg/mL) in *P. acnes* isolates from the US (5).

IN VITRO INFORMATION

Minocycline

Minocycline (CAS No. 10118-90-8) is a second generation semi-synthetic derivative of tetracycline with comparable antibacterial activity against a number of Gram-negative and Gram-positive organisms, including tetracycline-resistance organisms. Minocycline was patented (US) in 1965, and the hydrochloride salt (CAS No. 13614-98-7) is chemically defined as [4S-(4a, 4aa, 5aa, 12aa)]-4, 7-bis (dimethyl- amino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 10, 12, 12a-tetra hydro-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride.

Minocycline has a chemical formula of $C_{23}H_{27}N_3O_7$ and a molecular weight of _____ [_____ for the mono-hydrochloride, CAS No. 13614-98-7]. Minocycline has a high lipid solubility with an octanol/water partition coefficient (K_{ow}) = 1.1 compared to tetracycline (K_{ow} = 0.036) or doxycycline (K_{ow} = 0.60).

Minocycline HCL _____ contain 45, 90, or 135 mg of minocycline. The proposed clinical indication is for treatment of inflammatory lesions associated with moderate-to-severe acne vulgaris. The recommended dose will be 1 mg/kg/day (0.76-1.50 mg/kg/day), depending on the weight of the patient, or 29-57 mg/m²/day). Minocycline HCL _____ consist of active drug substance, minocycline (as the hydrochloride salt)USP, and the inactive ingredients _____, USP, lactose monohydrate NF, colloidal silicone dioxide NF, magnesium stearate NF, and an Opadry II film coating (grey, yellow, or pink at 12mg/ _____). These inactive ingredients are commonly recognized pharmaceutical excipients with a safe history of use in oral formulations. They all are listed in the FDA CDER Inactive Ingredients in Approved Drug Products administered by the oral route. These inactive ingredients are also considered to be GRAS for food use or are FDA approved as direct food or color additives (Section 2.4.1.3).

Pharmacokinetics (section 2.4.4)

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Minocycline is readily absorbed from the gastrointestinal tract (>95%) following a 100 to 200 mg oral dose (59 to 118mg/m²) with peak (C_{max}) serum concentrations of 2 to 6 µg/mL occurring 2 to 4 hours post-dose (T_{max}) and an apparent terminal elimination half-life of 14 to 18 hours. Because of its high lipid solubility, minocycline has a high volume of distribution (>80L). Minocycline binds moderately to human plasma proteins (70 to 80%). Minocycline is metabolized in the liver to 3 inactive metabolites (9-hydroxy-, N-demethyl-, and N₄-demethyl-minocycline). The predominant route of excretion for minocycline (and metabolites) in humans is the feces.

Antimicrobial Spectrum of Activity

Tetracyclines are active against many gram-positive and gram-negative bacteria, mycoplasmas, chlamydiae, rickettsiae and some protozoa. Examples of organisms shown to be susceptible to minocycline are shown on Table 2.

Table 2. In Vitro Activity of Minocycline against a Variety of Bacteria (6)

Organisms (no of isolates)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>Eikenella corrodens</i> (18)	0.25	1
<i>Moraxella</i> sp (13)	0.125	0.25
<i>Pasteurella canis</i>	0.125	0.125
Miscellaneous gram negative bacteria ^a (13)	0.06	0.125
Gram positive non-sporeforming rods ^b (20)	0.125	0.25
<i>S. aureus</i> (15)	0.06	0.06
Coagulase negative staphylococci (18)	0.06	1
<i>Streptococcus</i> spp(23)	0.06	0.125

^a *Bordetella brochiseptica*; *Capnocytophaga* sp.; CDC NO-1; *Haemophilus aphrophilus*; *H. parainfluenzae*; *Neisseria cinera*

^b *Actinomyces israelii*; *A. naeslundii*; *A. neuii*; *A. pyogenes*; *A. viscosus*; *Eubacterium* spp; *Propionibacterium acnes*; *P. avidum*, *P. freudenreichii*, and *P. lympholyticum*

Mechanism of Action

Tetracyclines are broad spectrum antibiotics with the hydronaphthacene nucleus containing four fused rings. The congeners from three groups based on the duration of action. Chlortetracycline, oxytetracycline, and tetracycline are short acting while doxycycline and minocycline are long acting.

Tetracyclines exert its action against susceptible organisms by inhibiting protein synthesis. They bind reversibly to the 30S ribosomal subunits of the bacteria, blocking

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the access of aminoacyl-tRNA to the RNA-ribosome complex, thereby preventing bacterial polypeptide synthesis. The action is bacteriostatic.

Minocycline has high lipid solubility enabling it to penetrate the bacterial cell wall to a greater extent than other members of this class.

Antimicrobial Resistance

The drugs in the tetracycline class have similar antimicrobial spectra and cross-resistance among them is common. Bacteria utilize three strategies to become resistant to tetracyclines. These are limiting access to the ribosome (efflux), altering the ribosome to prevent effective binding of tetracycline and producing tetracycline-inactivating enzymes (7). Strains of bacteria carrying combinations of efflux and ribosome protection genes have been found (7).

IN VIVO INFORMATION

The efficacy of the modified-release formulation of minocycline HCL was determined from the results of one Phase 2 placebo-controlled dose-ranging study (MP-0104-01) and two Phase 3 placebo-controlled efficacy and safety studies (MP-0104-04 and MP 0104-05). Results from a study to determine the relative antimicrobial effects of the new modified-release formulation of minocycline against *P. acnes* (MP-0104-09) were provided.

SYNOPSIS AND REPORTS OF CONTROLLED CLINICAL STUDIES

The synopsis of Phase 3 studies MP-0104-04 and MP-0104-05 are described here. Both studies were randomized, double-blind, placebo-controlled. Subjects were at least 12 years of age with inflammatory facial acne vulgaris ≥ 25 and >75 inflammatory facial lesions (papules and pustules) and <2 nodules/cysts on the face and a Global Severity score of moderate or severe were enrolled. Subjects weighed 45 kg to 136.36.kg (99 to 300 lbs). Minocycline HCL — 1mg/kg/day or placebo, once daily as 45 mg, 90 mg, and 135 mg — or identical control — were given to subjects. Treatment duration was for 16 weeks: 12 weeks' treatment and 4 weeks follow-up. The primary endpoints were: 1) per cent change from baseline in inflammatory lesions counts at Day 84 and 2) the proportion of subjects achieving success defined as: 0 (clear) or 1 (almost clear) based on the dichotomized Evaluator's Global Severity Assessment for inflammatory lesions only at day 84. Per cent change was calculated as follows:

$$\left[\frac{\text{Baseline lesion count} - \text{post-baseline lesion count}}{\text{baseline lesion count}} \right] \times 100$$

In study MP-0104-04, there were 300 subjects that entered the study group, 149 completed; 151 subjects entered in the placebo control group, 79 completed the study. In

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study MP-0104-05, there were 315 subjects that entered the study group, 171 completed; 158 subjects entered in the placebo control group, 76 completed the study. In comparing minocycline to placebo, superiority was achieved if both of these analyses were statistically significant in favor of minocycline. This data is seen in Table 3.

Primary endpoints were the percent reduction in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12 (end of treatment) and the proportion of subjects who had an investigator’s “Static Global Assessment” score of 0 or 1 at week 12. The secondary endpoints were the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from baseline to week 12; and the change in the subject’s “Global Assessment” from baseline to week 12; the proportion of subjects with a Subject’s Global assessment score of 0 or 1 at week 12 and the time to a 50% reduction in total lesion counts.

Primary Efficacy Results

Table 3. Inflammatory Lesion Counts at Day 84- ITT Population (2.5.4.4.1)

	MP-0104-04		MP-0104-05		Pooled	
	<u>Minocycline</u> <u>N=300</u>	<u>Placebo</u> <u>N=151</u>	<u>Minocycline</u> <u>N=315</u>	<u>Placebo</u> <u>N=158</u>	<u>Minocycline</u> <u>N=674</u>	<u>Placebo</u> <u>N=364</u>
<u>Baseline</u>						
Mean +/-SD	39.1 ±13.3	38.7 ±13.0	38.9±11.66	38.4±11.82	38.9 ± 12.73	38.8±13.33
Median	35.0	35.0	36.0	34.0	35.0	35.0
Range	24.0-81.0	23.0-87.0	20.0-82.0	25.0-82.0	20.0-92.0	20.0-94.0
p-value	0.789		0.847		0.698	
<u>Change from Baseline to Day 84</u>						
Mean +/-SD	16.5 ±15.07	12.3 ±15.78	17.2 ±13.65	11.3± 18.09	17.3 ±14.65	12.6±17.84
Median	18.0	14.0	19.0	12.5	18.0	14.0
Range	-64.0-66.0	-59.0-67.0	-26-65	-93.0-77.0	-64.0-70.0	-93.0-83.0
p-value	N/A		N/A		N/A	
<u>Percent change from baseline to Day 84</u>						
Mean +/-SD	43.1± 36.7	31.7± 40.3	45.8 ±34.84	30.8 ±46.96	45.5±35.63	32.4±43.63
Median	48.6	36.1	50.0	33.7	50.0	36.2
Range	-213.3-100.0	159.5-100.0	81.3-100.0	-310.0-100.0	-213.0-100	-310-100
p-value	0.001		<0.001		<0.001	

In Phase 3 studies MP-0104-04 and MP-0104-05, the mean and median absolute decreased in inflammatory lesion count and the per cent changes from baseline to Day 84 were greater in the minocycline group than in the placebo group. The primary efficacy analysis of the ITT population was the per cent change from Baseline to Day 84 which shows that the difference between the minocycline and placebo groups (shown in Table

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3) was statistically significant ($p=0.001$ in Study MP-0104-04 and $p<0.001$ in Study MP-0104-05). The pooled data also showed statistically significant difference ($p<0.001$).

The secondary primary endpoint in the Phase 3 studies was the proportion of subjects who achieved success, defined as a score of 0 (clear) or 1 (almost clear), on the dichotomized Evaluator's Global Severity Assessment (Inflammatory Lesions only) at Day 84. Table 4 shows the Evaluator's Global Severity Assessment grading criteria. In comparing minocycline to placebo, superiority was achieved if both of these analyses were statistically significant in favor of minocycline.

Table 4. Evaluator's Global Severity Assessment

Score *	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules most be resolving and may be hyper-pigmented, though not pink) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

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Results of the dichotomized analysis of the Evaluator's Global Severity Assessment are shown in Table 5.

Table 5. Evaluator's Global Severity Assessment (Inflammatory Lesions) Dichotomized as Success or Failure (Table 2.5.4.4.2 Section 2.5.4.4)

	Number (%) of Subjects in Success Category*					
	MP-0104-04		MP-0104-05		Pooled	
	Minocycline N=300	Placebo N=151	Minocycline N=315	Placebo N=158	Minocycline N=615	Placebo N=309
Day 28						
No. (%)	9(3.0)	0	13(4.1)	2(1.3)	22(3.6)	2(0.6)
<i>p</i> -value**	0.031		0.071		0.006	
Day 56						
No. (%)	25(8.3)	5(3.3)	38(12.1)	5(3.2)	63(10.2)	10(3.2)
<i>p</i> -value	0.036		<0.001		<0.001	
Day 84						
No. (%)	52(17.3)	12(7.9)	50(15.9)	15(9.5)	102(16.6)	27(8.7)
<i>p</i> -value	0.006		0.018		<0.001	

*Success is defined as Clear or Almost Clear (EGSA =0 or 1)

** *p*-value for treatment difference from Cochran-Mantel-Haenszel test

In the Phase 3 studies MP-0104-04 and MP-0104-05, the results showed that the proportion of subjects in whom treatment was determined successful increased over the course of the treatment period (Day 28, Day 56, Day 84) in both treatment groups. The results also showed that the proportion was twice as great in the minocycline-treated subjects as in the placebo subjects. The difference were statistically significant at Day 28 ($p=0.031$), Day 56 ($p=0.036$) and Day 84 ($p=0.006$) in Study MP-0104-04, and in Study MP-0104-05, Day 56 and Day 84, with $p = <0.001$ and 0.018 , respectively. The pooled data demonstrated similar results. The proportion of subjects considered to be treatment success increased from 3.6% at Day 28 to 16.6% at Day 84 in the minocycline group and from 0.6% at Day 28 to 8.7% at Day 84 in the placebo control group. The treatment difference at all 3 time points was statistically significant ($p \leq 0.006$)

SYNOPSIS OF STUDY MP-0104-09: An Evaluation of the Anti-microbial Effects in vivo of Minocycline — in Humans

The objective of the study was to determine the relative antimicrobial effects of a new modified-release formulation of minocycline by measuring its inhibitory action against *P. acnes* counts in vivo.

Secondary objectives were to determine

- Change in log *P. acnes* counts from Baseline to Weeks 4, 8 and 16

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- Percentage of subjects with Evaluator's Global Severity Assessment of clear or almost clear at each time point
- Percentage of subjects who achieve a 2-point improvement in Evaluator's Global Severity Assessment at each time point
- Percentage of subjects who show change in susceptibility to tetracycline, doxycycline or minocycline at Weeks 4, 8, 12 and 16
- Incidence of adverse events and clinically significant changes in clinical laboratory parameters.

The study was an open-label, 16 week, uncontrolled, single center study. The modified-release formulation of minocycline was administered in a 1 mg/kg/day dosing regimen in subjects with moderate-to-severe facial acne. The study was performed in the _____ The study consisted of a 12-week treatment phase and a 4 week follow-up phase. After screening and baseline evaluations, subjects returned to the clinic at Day 28, 56, and 84, and at Day 112.

The primary efficacy endpoint in this study was the change from Baseline to Day 84 in log *P. acnes* counts. The secondary efficacy endpoints included change from Baseline to Days 28 and 56 in log *P. acnes* counts; the percentage of subjects with an Evaluator's Global Severity Assessment of clear or almost clear at Days 28, 56, and 84; the number of subjects with a 2-point improvement in their Evaluator's Global Severity Assessment at Days 28, 56, and 84; the number and percentage of subjects with a change in *P. acnes* susceptibility from Baseline to Days 28, 56, 84, and 112.

There were 28 subjects enrolled in the study; 1 subject withdrew from the study before completing treatment and follow-up phases. All of the 28 subjects received at least 1 dose of study medication and were included in the Intent-to-Treat (ITT) analysis population. The ITT population included all subjects who received at least one dose of the study drug. Of the 28 subjects, 13 subjects (46.4%) were included in the Modified- Intent-to-Treat (MITT) population. The MITT population was the subgroup of ITT subjects who showed baseline *P. acnes* counts $>10^4$ CFUs/cm².

The total number of *P. acnes* counts was calculated as the sum of the absolute counts (prior to log transformation) from cheek and forehead cultures. Counts were log-transformed prior to analysis, except when the observations of zero absolute counts were observed, an analysis value of zero (0) was assigned.

Description of Microbiology Procedures

The Applicant provided description of the microbiology procedures performed in the Study Protocol MP-0104-09 (Section 6.1.1 and 6.1.2 study-report-mp-0104-09 Page 175 of 251).

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Collection of samples for quantitative cultures

Quantitative bacteriologic cultures were obtained from two test sites (forehead and cheeks) using published scrub procedures based on the Williamson and Kligman (8) technique for obtaining *P. acne* samples at baseline, and the 4, 8, 12 and 16 week visits.

Cup Scrub Method

The cup scrub method is performed by placing a 2.4 cm diameter glass wing tipped cup over the area. Into this cup, 5 mL of sterile ——— buffer containing 1% Triton X-100 sampling solution is added. The area is massaged with a rounded end glass rod for 1 minute. The sampling fluid is removed with a sterile pipette and transferred to a sterile sample tube. This procedure is repeated and performed on the left and right sides of the forehead and cheek areas.

The cup scrub fluid is then diluted by transferring 1 mL of the sampling fluid into a 9 mL phosphate buffer tube (1:10 dilution). All dilutions are plated on anaerobic blood agar in duplicate by the spiral plate method and incubated under anaerobic conditions using ——— anaerobic systems with carbon dioxide generators for 7 days at 35° +/-2°C.

Incubation and Counting of *P. acnes*

After 7 days of incubation, representative colonies from each of the panelist plates are streaked for isolation onto brain heart infusion agar plates and incubated for a minimum of 48 hours under anaerobic conditions. Gram stains are performed on all representative colonies and identifications are conducted on gram positive bacillus. Identifications are performed using the ——— on the colonies to determine if *P. acnes* are present. The representative colonies from the original dilution plate are counted using the counting guidelines supplied with the ——— spiral plating system manual enumeration of spiral plates.

The *P. acnes* CFU enumerated during the screening visit are considered baseline values for the study. Subjects whose plates have both *P. acnes* present and a baseline count >104 of the organism per square centimeter will be part of the modified intent-to-treat for analysis purposes. The procedure was repeated at 4, 8, 12 and 16 weeks.

Susceptibility Cultures

In addition to the above cultures, at baseline, Week 4, 8, 12 and 16, samples were plated in Brucella agar — with tetracycline, doxycycline and minocycline incorporated at

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Date review Completed: 3 Apr 06

1µg /ml. If growth occurs, the representative cultures will be plated on agar with 2, 4, 8, 16, 32, 64 and 128 µg of antibiotic.

Reviewer's Comments:

The microbiology procedures described in this application (N50-808 Sec 6.1.1 and 6.1.2) used to perform the experiments in the Study Protocol MP-0104-09 were previously reviewed. The following clinical microbiology comments and queries were forwarded to the Sponsor and the review can be found in IND 65 398 SN0017 submission (3 September 2004).

- 1) The Sponsor did not provide any information regarding preservation of samples during transport. The Sponsor's reason is that, Medicis plans to use sites that have the capability to culture and analyze the samples at their facility.

The Sponsor does not provide the time criteria for specimens to reach the laboratory for culture processing. If delay in processing is anticipated, it is recommended that samples are placed in appropriate anaerobic transport media that have been evaluated for use with anaerobic gram -positive rods.

Question to the Sponsor:

How does the Sponsor plan to verify that organisms remain viable when the samples reach the laboratory without the aid of a transport medium or anaerobic transport system?

- 2) The Sponsor states that "the representative colonies are counted using a _____ Colony counter to help differentiate between colonies of *P. acnes*. This portion of the procedure is not clear.

Questions to the Sponsor:

*Does the Sponsor plan to perform the colony count on the 7 day old culture medium (original plate) after *P. acnes* is identified? Explain how the _____ Colony counter would differentiate or identify colonies of *P. acnes*?*

- 3) In the Sponsor's description of the procedures (6.1.1 *P. acnes* cultures page 16 paragraph 3), the Sponsor states that: "All dilutions are plated on anaerobic blood agar in duplicate by spiral plate method and incubated under anaerobic conditions using _____ anaerobic systems with carbon dioxide generators for 7 days at 35 +/-2 degrees C."

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The Reviewer reminds the Sponsor that samples collected from the target sites may be contaminated with skin indigenous flora, some of which are facultative anaerobic organisms. These may include coagulase-negative staphylococci (CoNS) and facultative anaerobic diphtheroids. Incubation of anaerobic cultures for 7 days may allow sufficient growth and isolation of the obligate anaerobe *P. acnes*. However, growth of less fastidious species such as CoNS and facultative anaerobic diphtheroids occurs at a faster rate than most anaerobes and may therefore tend to over-grow *P. acnes*. Most anaerobic cultures are examined within 48-72 hours for growth and identification.

Question to the Sponsor:

What is the Sponsor's rationale for the 7 day incubation period? How does the Sponsor plan to prevent the over growth of other species in the culture?

Response to the comments and queries mentioned above were not provided by the Sponsor in any subsequent IND submissions. The procedures described in this application presented similar questions concerning the performance of isolation, recovery, semi-quantitation, and identification of *P. acnes* recovered from cultures.

Conclusions

The appropriateness of the microbiology procedures is difficult to assess because of the issues and questions that remained unanswered. The Applicant proceeded with the protocol without responding to the queries forwarded by the Clinical Microbiology Reviewer.

Global Severity Assessment and *P. acne* counts

Table 6 shows the results of the Evaluator's Global Severity Assessment [Table 10.3.1 page 31 Study Protocol report MP-0104-09 (N50-808)] that indicates a decrease in acne severity through the 12-week (Day 84) treatment period. At baseline, all 28 subjects enrolled were assessed with moderate or severe acne, 96.4% (27/28) and 3.5% (1/28), respectively. By Week 12 (Day 84), 77.8% (21/28) of subjects showed mild acne and 11.1 % (3/28) were almost clear. There were no subjects that were completely clear at any time point.

Table 6. Evaluator's Global Severity Assessment (ITT Population)

	N (%) Almost Clear	N(%)Mild	N(%)Moderate	N (%) Severe	N (%) 2-point improvement
Baseline	0	0	27 (96.4)	1 (3.6)	---
Day 28 (Wk4)	0	13 (46.4)	14 (50.0)	1 (3.6)	0

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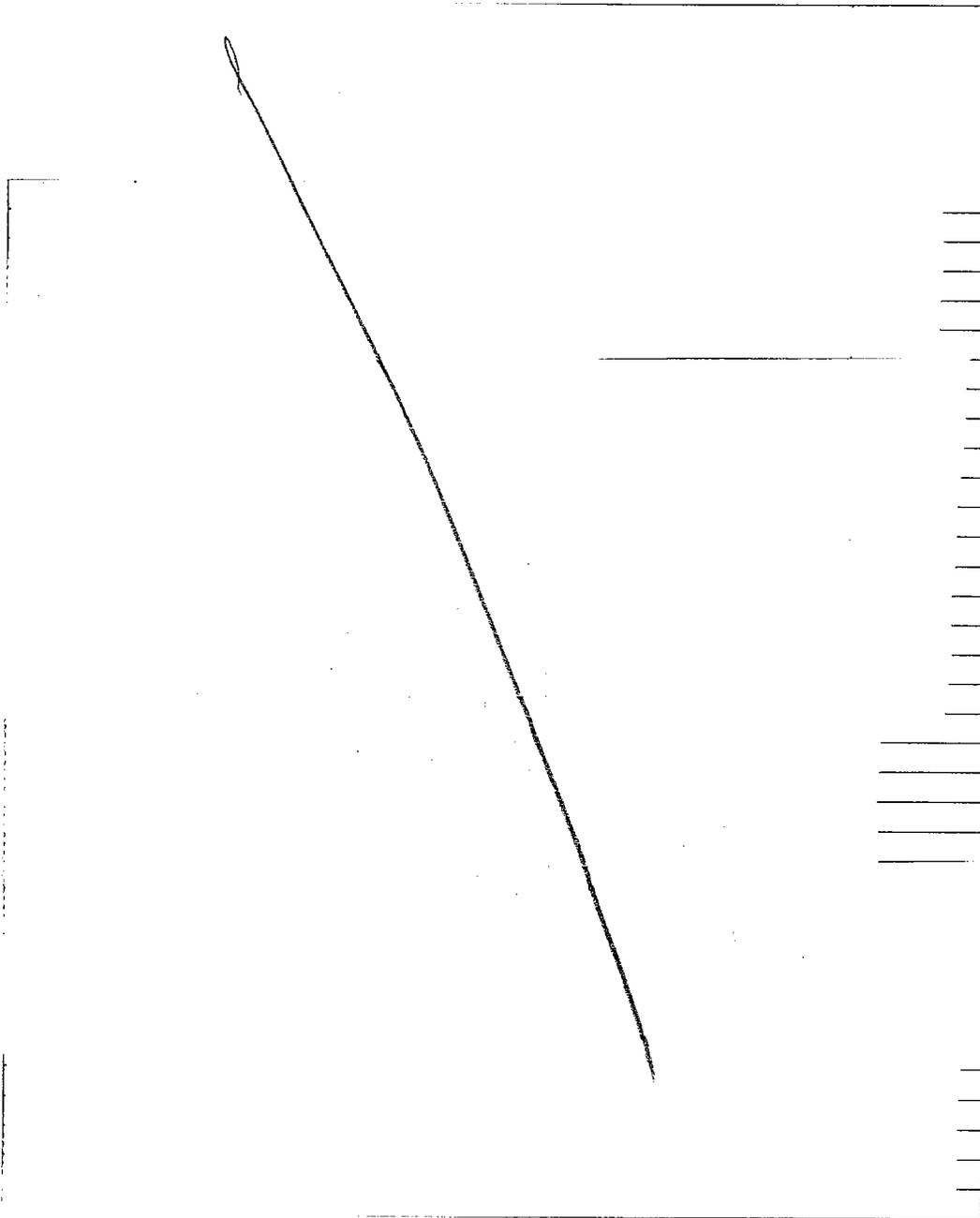
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 Deliberative Process

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Conclusion

The results in Table 7 indicate that culture results are independent of the severity of acne. At week 8, 40% (10/25) of those with negative cultures were evaluated with mild acne and 44% (11/25) with moderate acne. At week 12, the extent of improvement in the severity assessment was similar among subjects with negative *P. acnes* culture compared with

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subjects with positive *P. acnes* cultures. While there may be a relationship between reduction in *P. acnes* and clinical benefit the fact that culture results and the presence or absence of clinical acnes were independent of each other in this study is not unique in that this has been reported in the literature (9).

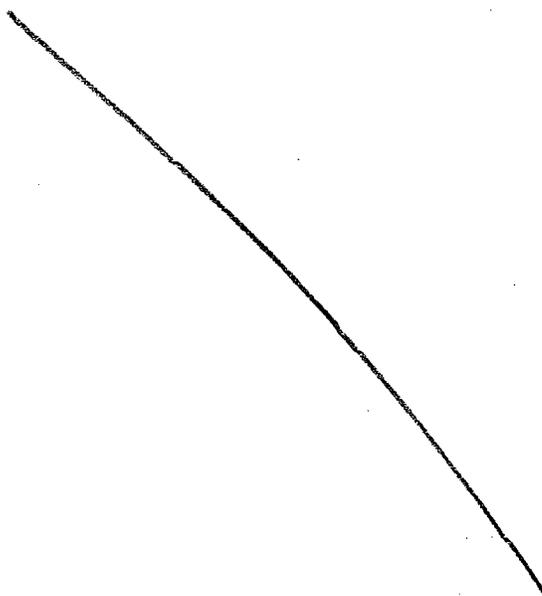
OVERALL CONCLUSION

Propionibacterium acnes is a strictly anaerobic gram-positive bacillus that has been associated with acne vulgaris. Microbiology studies performed during the clinical studies attempted to determine the relative antimicrobial effects of the modified-release formulation of minocycline by measuring its inhibitory effects against *P. acnes* in vivo.

The results of the clinical studies performed by the Applicant, met the primary and secondary clinical efficacy evaluation criteria. However, the study to show correlation between *P. acnes* colony counts in culture with severity assessment scores indicated that culture results are independent of the severity of acne assessment scores.

From a microbiology perspective the product is approvable with the following changes to the "Indication" and "Microbiology" sections of the package insert (See Agency's proposed "INDICATION" and "MICROBIOLOGY" sections of package insert below).

APPLICANT'S PROPOSED PACKAGE INSERT



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REFERENCES

1. Healy E, N Simpson. 1994. Fortnightly review of acne vulgaris. *BMJ* **808**:831-833.
2. Lee D, G VanDyke, J Kim. 2003. Update on pathogenesis and treatment of acne. *Current Opinion in Pediatrics* **15**:405-410.
3. Webster G. 2002. Acne vulgaris. *BMJ* **325**:475
4. Leyden J. 1997. Therapy for acne vulgaris. **336**:1156-1162.
5. Ross JL, AM Snelling, EA Eady, et al. 2001. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, USA, Japan, and Australia. *Br J Dermatol* **144**:339-346.
6. Goldstein E, D Citron, CV Merriam, et al. 2000. Comparative in vitro activities of GAR-936 against aerobic and anaerobic animal and human bite wound pathogens.

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Antimicrob Agents Chemother **44**:2747-2751.

7. Speer BS, NB Shoemaker, AA Salyers. 1992. Bacterial resistance to tetracyclines: mechanisms, transfer, and clinical significance. Clin Microbiol Rev **5**:387-399.

8. Williamson P, AM Kligman. 1965. A new method for quantitative investigation of cutaneous bacteria. *JAMA* **45**:498-503.

9. Leyden JJ. 2001. The evolving role of *Propionibacterium acnes* in acne. Seminars in Cutaneous Medicine and Surgery **20**:139-143.

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Fred Marsik, Ph.D.
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FIN 4/17/06 FJM

* C. Mahon did the initial draft review. The review was completed by F. Marsik due to the departure of C. Mahon from HFD-520.

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/s/

Frederic Marsik
4/17/2006 12:18:49 PM
MICROBIOLOGIST

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW CONSULTATION
FOR HFD 540**

IND 65 398 SN 032 Minocycline ER _____ :

Date Company Submitted: 26 February 2005
Date Received (HFD 520) : 7 March 2005
Date Assigned: 7 March 2005
Date Completed: 16 March 2005
Reviewer: Connie R. Mahon, MS

NAME AND ADDRESS OF APPLICANT:

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DRUG PRODUCT NAME

Established Name: Minocycline hydrochloride
Code Name/Number: None
Chemical Name: 4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride
Chemical formula: $C_{23}H_{27}N_3O_7 \cdot HCL$
Molecular Weight: ~~462.5~~

PROPOSED INDICATION:

Primary treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.

PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF

ADMINISTRATION, AND DURATION OF TREATMENT: Oral 45, 90, 05 135 mg of minocycline; 1 mg/kg/day (0.76-1.50 mg/kg/day), depending on the weight of the patient (29-57 mg/m²/day

Duration of treatment: Not indicated

TYPE OF SUBMISSION:

Microbiology Review Consult for HFD 540

In the proposed indication, the Minocycline HCL ~~_____~~ will contain 45, 90, or 135 mg of minocycline. The intended clinical indication is for the treatment of inflammatory lesions associated with moderate-to-severe acne vulgaris. According to the Sponsor, this new formulation may reduce or prevent vestibular side effects often associated with the rapid absorption and bioavailability that occurs with immediate-release formulations of minocycline. Altered oral dosage regimens with minocycline apparently have been reported to reduce vestibular side effects.

In this submission, the Sponsor provides a list of specific questions and asks guidance from the Agency regarding compilation and presentation of the material. There are no questions that specifically address microbiology; however, studies that pertain to microbiologic activity of minocycline are provided under pharmacology. Under non-clinical studies, Pharmacology, the Sponsor describes the mechanism of action of tetracyclines as broad-spectrum bacteriostatic agents. Tetracycline inhibits protein synthesis by binding aminocyl-t-RNA binding to the m-RNA ribosome complex. Because of its high lipid solubility, minocycline penetrates the bacterial cell wall to a greater extent than other members of this chemical class as related to increased antibiotic activity. The Sponsor reports that, similar to other antimicrobials, resistance to minocycline can occur, and is likely through an altered ribosome (*tet* gene). This appears to be rare (<1%) with use of minocycline against *Propionibacterium acnes*. The Sponsor also provides a "Microbiology Antibiotic Profile". This profile lists the various bacterial species and other organisms that have demonstrated in vitro susceptibility to minocycline. The Sponsor describes the activity of minocycline against *P. acnes* from published literature. (IND 65,398 26 Feb 2005, Section 2.4.2 pages 15-16).

Under Ongoing Studies, the antimicrobial study entitled, "An Evaluation of the Antimicrobial Effects in vivo of Minocycline ~~_____~~ in Humans" that was started on 15 September 2004 enrolled 30 subjects. The primary objective of the single center, open label study is to determine the log change in *P. acnes* counts from baseline to end of treatment period (wk 12). Secondary objectives of the study include

- Log change in *P acnes* counts from baseline to Wk 4, 8, and 16
- Per cent of patients with an Evaluator's Global Severity Score of clear or almost clear, or those patients who achieve a 2 point improvement in scoring after 12 weeks
- Number and per cent of patients who show change in susceptibility to tetracycline, doxycycline or minocycline at wk 4,8,12, and 16.

The Sponsor plans to submit the full study report in July 2005.

CONCLUSION AND RECOMMENDATIONS: To be communicated to the Sponsor

Based on the information provided in this briefing package, from the microbiology perspective, the Sponsor is reminded to submit a draft of the language they propose to use in the Microbiology section of the proposed package insert for review. Correlation summaries of microbiology outcome and clinical response should be provided. The change in microbial counts of *P. acnes* from baseline to end of therapy in patients

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/s/

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3/31/05 08:15:14 AM
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MEDICAL OFFICER