

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-808

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER
/

NAME OF APPLICANT / NDA HOLDER
Medicis Pharmaceutical Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SOLODYN

ACTIVE INGREDIENT(S)
Minocycline Hydrochloride

STRENGTH(S)
45 mg, 90 mg or 135 mg

DOSAGE FORM
Modified Release —

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,908,838

b. Issue Date of Patent
6/1/1999

c. Expiration Date of Patent
2/19/2018

d. Name of Patent Owner
Medicis Pharmaceutical Corporation

Address (of Patent Owner)
8125 N. Hayden Road

City/State
Scottsdale, Arizona

ZIP Code
85258

FAX Number (if available)
602 808 3895

Telephone Number
602 808 8800


E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

Medicis Pharmaceuticals
8125 N. Hayden Road

City/State
Scottsdale AZ

 R. Todd Plott, MD, Vice President Clinical
Research and Regulatory Affairs

ZIP Code
85258

FAX Number (if available)
602 808 3895

Telephone Number
602 808 8800

E-Mail Address (if available)
tplott@medicis.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 1-6, & 10-15 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) The product is indicated for the treatment of acne.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

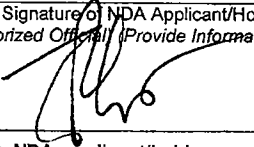
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



6/21/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name R. Todd Plott, MD, Vice President Clinical Research and Regulatory Affairs	
Address 8125 N. Hayden Road	City/State Scottsdale AZ
ZIP Code 85258	Telephone Number 602 808 8800
FAX Number (if available) 602 808 3895	E-Mail Address (if available) tplott@medicis.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 50-808 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 8, 2005 Action Date: May 8, 2006

Trade and generic names/dosage form: Solodyn (Minocycline Hydrochloride) Modified Release _____ 45 mg, 90 mg & 135 mg

Applicant: Medicis Therapeutic Class: S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. 0 yr. 0 Tanner Stage _____
Max _____ kg _____ mo. 0 yr. 11 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Felecia Curtis, RN
Regulatory Project Manager

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stanka Kukich
10/5/2005 05:07:45 PM



DEBARMENT AND FELONY CONVICTION CERTIFICATION

**Pursuant to Sections 306(a) and (b) of the
Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335(a) and (b))**

**SOLODYN® (Minocycline Hydrochloride) Modified Release (_____
45 mg, 90 mg and 135 mg**

This is to certify:

1. that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with the development or submission of this application;
2. that we will not use in any capacity the services of any person debarred under subsection (a) or (b) of this section in connection with this application; and
3. that neither the applicant nor affiliated persons responsible for the development or submission of this application have been convicted within the past (5) years of offenses described in subsections (a) and (b) of this section.

List of Convictions: none.

A handwritten signature in black ink that reads "R. Todd Plott".

R. Todd Plott, M.D.
Vice President
Clinical Research and Regulatory Affairs

6/7/05
Date



May 8, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Electronic DOCUMENT ROOM
5901-B Ammendale Road
Beltsville, MD 20705-1266

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to the New Drug Application (NDA) for SOLODYN™ (minocycline hydrochloride) submitted in accordance with 21 CFR 314.50 on June 30, 2005. Further reference is made to this morning's telephone contacts requesting additional changes to the package insert labeling.

Enclosed please find a formal submission of the final package insert labeling documenting our acceptance of FDA's requested changes.

Should you have any questions or need additional information, please contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

A handwritten signature in black ink that reads "R. Todd Plott".

R. Todd Plott, M.D.
Vice President
Clinical Research and Regulatory Affairs

mw

MEMORANDUM OF TELECON

DATE: April 21, 2006 1:30 PM

APPLICATION NUMBER: NDA 50-808

DRUG PRODUCT: Solodyn™

BETWEEN:

Division of Dermatology and Dental Products, HFD-540
Shirkant Pagay, PhD/Chemistry Reviewer, ONDQA
Felecia Curtis, Regulatory Project Manager

AND

Attendees via teleconference:

Medicis
Diane Stroehmann, RAC, Regulatory Affairs Associate
Todd Plott, MD, VP Clinical Research and Regulatory Affairs
Bhiku Patel, PhD, Executive Director, Product Development
Waranush Jitraphai, PhD, Senior Research Scientist
Thomas Siebenaler, Associate Director, Quality Control

1-877-847-8112 code 6028083851

SUBJECT: NDA 50-808/ Dissolution Test Specifications:

A teleconference was initiated by the Agency to request response from Medicis for the FDA's justification and to seek concurrence regarding the proposed regulatory specification for dissolution testing of Minocycline Extended Release Tablets.

Based on the review of the entire stability package and bioavailability studies, FDA would consider the following regulatory specifications (4/11/06).

1 hr..... %
2 hr..... %
4 hr..... %

The sponsor submitted the following response: (Amendment Date 4/19/06)

The stability data utilized in establishing the proposed dissolution specifications was collected from the bracketed stability testing of 3 registration batches of 45 mg (03290, 04007 and 04008) and 3 registration batches of 135 mg (03292, 04011 and 04012) tablets. Due to this limited amount of data, Medicis would like to retain the originally proposed dissolution specifications until additional data from the commercial manufacture of the 45 mg, 90 mg, and 135 mg tablets is obtained. Medicis commits to assessing the potential for adjusting the dissolution specifications upon completion of 24 months (expiry) of stability testing on the first 3 commercial production batches of each of the three strengths and submitting the data in an annual report to NDA 50-808.

FDA responded to the sponsor the following justification for the proposed Regulatory specifications for discussion with the sponsor via telecom:

- The use of bracketing concept assumes that the 45 mg and 135 mg minocycline extended release tablet strengths represent the same stability pattern as that of the 90 mg minocycline extended release tablet.
- The review data includes at least one batch of 90 mg minocycline extended release tablet used in Phase III clinical trials. (Page 93 - 103 Section 3.2.P.8).
- The stability data reviewed covers a large amount of individual tablet dissolution data at various storage time and temperature.
- The proposed regulatory specifications allows fall back to USP <711> Acceptance Table 2 level L₂ and level L₃, if 1 or 2 tablets fail the proposed regulatory acceptance criteria.
- The proposed regulatory specifications for the registration batches are considered to be representative of the Phase III clinical study batches.
- A wider dissolution acceptance criteria beyond the data obtained for the clinical/ registration batches is justified with appropriate formulation design including the boundary conditions and biopharmaceutical consideration

Based on FDA's justification for the proposed regulatory specifications for dissolution, the sponsor agreed with the FDA's proposal and will submit information requested in a timely manner to expedite the review process.

The conversation ended amicably.

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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
4/25/2006 02:11:36 PM
CSO

Shrikant Pagay
4/25/2006 02:56:06 PM
CHEMIST



April 24, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Response to FDA Labeling Request

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the FDA faxed filing communication dated April 24, 2006, providing labeling comments for this NDA.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

Enclosed please find a detailed summary including FDA's comments in bold italics followed by Medicis' response to the April 24, 2006 fax.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww



April 21, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Response to FDA Request for CMC Information

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the FDA faxed filing communication dated April 21, 2006, requesting information pertaining to chemistry, manufacturing and controls sections of the NDA and the April 21, 2006 teleconference between FDA and Medicis representatives.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

Enclosed please find a detailed summary including FDA's comments in bold italics followed by Medicis' response to the April 21, 2006 fax.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

A handwritten signature in black ink that reads "R. Todd Plott".

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

dms



April 20, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Electronic DOCUMENT ROOM
5901-B Ammendale Road
Beltsville, MD 20705-1266

**Phase 4 Commitment
Request**

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to the New Drug Application (NDA) for SOLODYN™ (minocycline hydrochloride) submitted in accordance with 21 CFR 314.50 on June 30, 2005. Further reference is made to the April 19, 2006, fax from FDA stipulating the Phase 4 Commitments for this NDA.

Medicis commits to submit results of ongoing 2-year, open-label safety study (MP-0104-07) and the 2-year open-label growth study in pediatric subjects within 3 months after study completion to the Agency.

Protocol Submission:	Originally submitted to IND on 8/20/03
Study Start:	Study is ongoing
Final Report Submission:	May 2007

Medicis commits to conduct an appropriate designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis. The spermatogenesis study will be appropriately representative of US demographics and will include a more racially diverse population.

Protocol Submission:	Submitted to IND for SPA on 12/16/05. The Agency responded and accepted the request on February 1, 2006. Medicis commits to submitting the final protocol in July 2006.
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Study Start:	September 2006
Final Report Submission:	December 2007

Medicis commits to conduct non-clinical rat and mice carcinogenicity studies. Draft protocols will be submitted to the FDA for review by the CAC in May 2006. Medicis commits to begin the studies no later than three months after agreement between the FDA and Medicis regarding the proposed protocols.

NDA 50-808
SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg
Response to FDA's April 19, 2006 Phase 4 Commitments Request

Medicis Pharmaceutical Corporation
April 20, 2006

Protocol Submission:	May 2006
Study Start:	Three months from agreement between FDA and Medicis on protocols.
Final Report Submission:	Three months from completion of Final Study Report.

Medicis commits to conduct an evaluation of carcinogenicity of minocycline HCl in mice and rats.

The non-clinical rat and mice studies will include a 2-year in-life portion, followed by approximately one year of study analyses and histopathology by the laboratory conducting the studies. Following that, Medicis will conduct an evaluation of carcinogenicity. The time required for that evaluation is dependent upon the results of the studies and may take up to one year to complete. Medicis commits to send updates on the progress of these studies at 6-month intervals following the commencement of these studies and to provide the final report within 3 months of its completion.

Protocol Submission:	May 2006
Study Start:	Three months from agreement between FDA and Medicis on protocols.
Final Report Submission:	Three months from completion of Final Study Report.

Should you have any questions or need additional information, please contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President
Clinical Research and Regulatory Affairs

fww

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FDA Fax Memo

Date: April 19, 2006

Subject: NDA 50-808 Phrase 4 Commitments

Hi Michelle,

The Agency requests that you review, provide dates and commit to the phrase 4 commitments that are listed below. Please provide a letter stating that you agree to the following phrase 4 commitments with the commitment include in the body of your agreement letter.

1. Submit results of ongoing 2-year, open-label safety study (MP-0104-07) and the 2-year open-label growth study in pediatric subjects within 3 months after study completion to the Agency.

Protocol Submission:

Study Start:

Final Report Submission:

2. Conduct an appropriately designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis within 3 months of drug approval and submit results to agency within 3 months after study completion. The spermatogenesis study should be appropriately representative of US demographics and should include a more racially diverse population.

Protocol Submission:

Study Start:

Final Report Submission:

3. Conduct non-clinical rat and mice carcinogenicity studies within 3 months of drug approval and submit results to the Agency within 3 months after study completion.

Protocol Submission:

Study Start:

Final Report Submission:

4. Evaluation of the carcinogenicity of minocycline HCl in mice.

Protocol Submission:

Study Start:

Final Report Submission:

5. Evaluation of the carcinogenicity of minocycline HCl in rats.

Protocol Submission:

Study Start:

Final Report Submission:

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FDA Fax Memo

Date: April 19, 2006

Subject: **NDA 50-808 Shelf Life Comment**

Hi Michele,

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The proposed shelf life for the drug product is 24 months. The long term storage data provided is 6 months in blister package and 6 months in 100 mL bottles. Based on the stability data and regression analysis, the lowest shelf life prediction is 12 months. It is difficult to predict dissolution changes from the limited information due physical changes not predictable based on kinetics. The division considers a shelf life of 12 months with annual reporting of increased shelf life based on the actual stability results.

Please submit this information by COB on April 20, 2006. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Respectfully,
Felecia Curtis

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/s/

Felicia Curtis
4/19/2006 08:42:48 AM
CSO



April 18, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Response to FDA Request for Information

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the FDA faxed filing communication dated April 17, 2006, requesting information pertaining to chemistry, manufacturing and controls sections of the NDA.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

Enclosed please find a detailed summary including FDA's comments in bold italics followed by Medicis' response to the April 17, 2006 fax.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

dms

FDA Fax Memo

Date: April 17, 2006

Subject: NDA 50-808 Dissolution Comment to the Applicant

Hi Michele,

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The dissolution data for all stability batches and clinical batches were reviewed by both the Divisions of Clinical Pharmacology and Chemistry. Both the high and the low dissolution value (% dissolved for individual tablet) are listed in the following table. The results represent the lowest and the highest % dissolved of individual tablet from the stability data of \ batches stored for 12 months at 25°C/60% RH and 6 months at 40°C/75% RH. The 6 months at 40°C/75% RH data are listed in (). The proposed dissolution specifications by the applicant are also listed.

Table with 3 columns: Time, Proposed, Actual Data. Rows for 1 Hour, 2 Hour, 4 Hour. Proposed values are NLT. Actual data cells contain scribbles.

Based on the review of the entire stability package and bioavailability studies, FDA would consider the following regulatory specifications.

1 hr
2 hr.....
4 hr.....

Extended-Release Dosage Forms

Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to Acceptance Table 2. Continue testing through the three levels unless the results conform at either L1 or L2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.

1 Page(s) Withheld

 X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-_____

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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
4/17/2006 10:43:26 AM
CSO



April 7, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to FDA's fax dated April 6, 2006 from Felecia Curtis including FDA's requested labeling changes to the package insert for this product, and to the subsequent communications between Ms. Curtis and Michelle Wells on April 7, 2006.

Pursuant to 21 CFR 314.60, Medicis hereby submits changes to the package insert as follows: 1) delete the p-values from Table 1, line 75, and 2) revise to "can not" (two words) on line 281, and 3) revised to "drug-resistant bacteria as well as" in lines 7 and 87. This submission also includes a complete set of mock final container and carton labels.

To facilitate review, this submission contains a table of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww



April 6, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Amundson Road
Beltsville, MD 20705

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to FDA's fax dated April 6, 2006 from Felecia Curtis including FDA's requested labeling changes to the package insert for this product.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

To facilitate review, this submission contains a table of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM: Felicia Curtis, Regulatory Project Manager,
Division of Dermatology and Dental Drug Products,
301-827-2043

DATE
08/22/2004

IND NO.

NDA NO.
50-808

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
06/30/2005

NAME OF DRUG
Solodyn (minocycline
hydrochloride) Modified
Release

PRIORITY CONSIDERATION
Target date 02/07/2006

CLASSIFICATION OF DRUG
3S

DESIRED COMPLETION DATE
01/15/2006

NAME OF FIRM: Medicis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the sponsor's requested trade name of Solodyn. PI, carton and container labels are attached.

PDUFA DATE: 05/08/2006

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA

HFD-540/Division File

HFD-540/RPM

HFD-540/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

Felicia Curtis 301-827-2043

METHOD OF DELIVERY (Check one)

DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

4 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-_____



March 30, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Information Request
Response**

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to FDA's faxes dated March 22 and 29, from Mary-Jean Kozma-Fornaro and Felecia Curtis, respectively, requesting information to be included in the label.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

A handwritten signature in black ink that reads "R. Todd Plott" with a stylized flourish at the end.

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

mw

FDA Fax Memo

Date: March 29, 2006

Subject: **NDA 50-808 Clinical IR**

Hi Michele,

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

"The Agency would like to inform the Sponsor as to where the information regarding thyroid papillary cancers arising in the setting of minocycline-induced black thyroid will be included in the label. The sponsor is referred to the article in Current Surgery, Volume 58, Issue 5, September-October 2001, pages 470-471 by Christian Birkedal, William J. Tapscott et al. titled - Minocycline-induced black thyroid gland: Medical curiosity or a marker for papillary cancer?"

Please submit this information by COB on March 31, 2006. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Respectfully,
Felecia Curtis

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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
3/29/2006 02:20:11 PM
CSO



March 22, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to FDA's fax dated March 20, 2006 from Mary-Jean Kozma-Fornaro including FDA's requested labeling changes to the package insert for this product.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

To facilitate review, this submission contains a table of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Additionally, reference is made to the March 22, 2006 FDA faxed communication from Mary Jean Kozma-Fornaro, requesting additional information for the labeling on this product regarding black thyroid. Medicis will address this request under separate cover shortly.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

NDA 50-808

March 22,2006

Clinical Information Request

Please inform the Agency as to where the information regarding thyroid papillary cancers arising in the setting of minocycline-induced black thyroid will be included in the label. The sponsor is referred to the article in Current Surgery, Volume 58, Issue 5, September-October 2001, pages 470-471 by Christian Birkedal, William J. Tapscott et al. titled - Minocycline-induced black thyroid gland: Medical curiosity or a marker for papillary cancer?

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/s/

Mary Jean Kozma Fornaro
3/22/2006 01:05:59 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 16, 2006

TO: Stanka Kukich, M.D., Acting Director
Director, Division of Dermatologic and Dental Products

VIA: Felecia Curtis, Regulatory Health Project Manager
Division of Dermatologic and Dental Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication
Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication
Support

SUBJECT: DSRCs Review of Patient Labeling for Solodyn
(minocycline HCL) Extended-release Tablets, NDA 50-808

Background and Summary

The sponsor submitted a PPI for review March 10, 2006, in response to an Agency request for patient labeling for Solodyn (minocycline HCL) Extended-release Tablets, NDA 50-808. Solodyn is indicated "for the treatment of non-nodular inflammatory lesions of moderate-sever-acne vulgaris in patients 12 years and older."

See the attached for our recommended revisions to the submitted Patient Labeling. We have simplified the wording, made it consistent with the PI, and removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

**Appears This Way
On Original**

Comments and Recommendations

We also have the following comment:

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division.

Please call us if you have any questions.

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4 Page(s) Withheld

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-_____

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
3/16/2006 01:35:41 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/17/2006 12:03:38 PM
DRUG SAFETY OFFICE REVIEWER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

PID#: _____

DATE: March 16, 2006

FROM: Hyon J. Kwon, Pharm.D., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation (DDRE)

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director,
Division of Drug Risk Evaluation (DDRE)
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation (DDRE)

TO: Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (DDDP)

SUBJECT: Drug: Solodyn™ (Minocycline Hydrochloride) [NDA 50-808]
Adverse Events: Death, hepatotoxicity, lupus, skin/photosensitivity, anaphylactic
reactions, and congenital anomaly

1. EXECUTIVE SUMMARY/INTRODUCTION

This consult is in response to a request made by DDDP to review adverse events associated with minocycline. A supplement was submitted by Medicis for approval of its modified release minocycline _____ Solodyn™, for acne therapy.

As of January 20, 2006, the AERS database contained 4795 adverse event reports associated with minocycline use, of which 733 were reports of adverse events in acne. Since DDRE performed a comprehensive review of minocycline dated April 21, 2004 (NDA No. _____/50-445/50-451/50-649/50-315/ _____ /50-444), this consult will focus on reports of death, liver injuries, lupus, skin/photosensitivity reactions, and congenital anomaly as specified by the requesting medical officer. In addition, we independently reviewed reports of anaphylactic reactions. DDRE and DDDP agreed to limit the review to reports of minocycline use for acne, except for the congenital anomaly cases, where we reviewed all reported cases.

The 2004 review of minocycline summarized six death cases. Since then, four additional post-marketing cases reported death as an outcome in patients who received minocycline to treat acne. Three deaths occurred from unknown causes after the patients experienced unspecified hepatic reactions, and one was a suicide case.

Due to the volume of all liver injury reports and the need for a timely response, we concentrated our efforts on severe liver injuries, particularly liver failure cases. The AERS database contained 165 liver injury reports associated with minocycline use for acne; of these, nine unique cases were identified as severe liver injuries based on ODS Liver failure/cirrhosis search criteria (see section 4, Part II for description of this criteria). Six of nine cases reported hepatic failures. Four of six hepatic failure cases were associated with hypersensitivity syndrome and/or skin eruptions; one was an autoimmune hepatitis case that progressed to hepatic failure; and the last case was an unspecified acute hepatitis/hepatic failure. The remaining three liver injury cases included a case of autoimmune hepatitis with cirrhosis, granulomatous hepatitis, and an unspecified hepatitis with jaundice and encephalopathy. One pediatric patient died due to fulminant hepatic failure; another patient required emergent liver transplantation for recovery; and four other patients recovered.

Consistent with a literature review², we observed two patterns of hepatotoxicity with minocycline use in acne in our cases: 1) hypersensitivity reaction with a rapid onset of within one month of treatment, and 2) autoimmune hepatitis with a late onset of about a year or more therapy. The majority of our post-marketing cases (n=6) experienced severe liver injury within a month of minocycline therapy and were accompanied by skin eruptions and/or hypersensitivity-type of reaction.

We reviewed 18 post-marketing cases of lupus/lupus-like syndrome that reported death, hospitalization, and life-threatening outcomes. Most occurred in females and the time to onset ranged from two months to five years of minocycline therapy (median 24 months). Most patients presented with constitutional and musculoskeletal symptoms such as polyarthritis/arthralgia, fever, and/or rash. Concurrent liver involvement was reported in six patients (five had autoimmune hepatitis), and one patient experienced pulmonary lupus. The antinuclear antibodies were positive in 11 patients. The majority, 61% of patients, reported recovery or improvement following discontinuation of minocycline. One patient reported positive rechallenge.

Sixteen cases of skin eruptions, including four cases of rash due to photosensitivity reactions, were reviewed. The reports of skin eruptions not due to photosensitivity reactions included Stevens Johnson syndrome (3), erythema multiforme (4), bullous dermatitis/rash (4), and pustular rash (1). Eight patients recovered from the skin reactions, including one photosensitivity reaction case. However, two patients with bullous dermatitis did not recover from the event, with one patient requiring skin grafting on legs due to progressive, necrotic bullous degenerative lesions. One patient with erythema multiforme reported positive rechallenge.

We reviewed six cases of anaphylactic reactions reported with minocycline use for acne. Most occurred within one dose or the same day of initiating minocycline therapy. Serious outcomes were reported in all six cases; the event was life-threatening in two cases, resulted in hospitalization in two cases, and both life-threatening and hospitalization were reported in the remaining two cases. Four patients recovered and the outcomes in the remaining two patients were unknown.

Minocycline is labeled as pregnancy category D and its use is not recommended during pregnancy. The concern with the use of minocycline during pregnancy, as a tetracycline-class antibiotic, has been the effect on fetal tooth and skeletal development, which is reflected in the labeling. We reviewed 21 post-marketing congenital anomaly cases. Fourteen women reported minocycline use around the time of conception and/or during their first trimester of pregnancy, and one patient reported drug use during her second trimester. One case of possible paternal exposure occurred during the time of conception. The time of minocycline exposure in the five remaining cases was not reported. Some confounders were present: five women reported using concomitant drugs that are labeled pregnancy category D/X and two women reported potential environmental/occupational exposure. Five women chose to have elective abortions after discovering congenital anomaly in the fetus; and another woman miscarried a few weeks after discovering an absent fetal heart. Fifteen congenital anomalies (one possibly due to paternal exposure) were reported with live births, with five live births reporting limb abnormalities including missing hands and/or reduced forearms. Two infants died within one week of delivery.

In conclusion, we summarized reports of death, liver injuries, lupus, skin/photosensitivity, and anaphylactic reactions with the use of minocycline for acne. The proposed label for Solodyn™ contains language regarding adverse events related to liver, lupus, serious skin reactions, and photosensitivity. The Precautions section states that _____, and the Adverse Reactions Section listed “hepatitis, liver failure.” Of 165 total liver injury reports (note: raw number, may contain

duplicates) associated with minocycline use for acne, we reviewed nine unique cases of severe liver injuries, which included six liver failure cases. In our case series, one patient died due to fulminant hepatic failure; three patients reported death after experiencing unspecified hepatic reactions; one patient required an emergent liver transplant; another patient with acute hepatitis/liver failure did not recover; and four patients with lupus (two of whom also exhibited autoimmune hepatitis/hepatitis) did not recover from the adverse event. Given these reports of serious liver injury reactions in patients treated for acne, we recommend that a "Hepatotoxicity" section be placed in the Warnings of the label to inform prescribing practitioners that serious liver injury cases, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal), have been observed in the post-marketing setting. We also suggest adding autoimmune hepatitis to the label.

Our review of skin eruptions included severe cutaneous reactions - three cases of Stevens Johnson syndrome (SJS), four cases of erythema multiforme (EM), and four cases of bullous dermatitis/rash. One patient with bullous dermatitis required skin grafting due to progressive, necrotic lesions. In addition, we reviewed six cases of anaphylactic reactions, which represent a severe and life-threatening form of drug hypersensitivity; four of these were considered life-threatening. Based on these cases, we recommend adding a "Serious Skin/Hypersensitivity Reaction" section under Precautions, to inform prescribing practitioners that post-marketing cases of anaphylaxis and serious skin reactions (such as SJS and EM) have been reported. We concur with the current label information concerning lupus, and make no further recommendations based on our current review of post-marketing lupus cases reported with minocycline use for acne.

Lastly, all congenital anomaly reports associated with minocycline, regardless of its indication, were reviewed. The label advises against its use during pregnancy, with warnings about the effect on fetal tooth and bone. Although it is often difficult to determine specific causality for birth defects since multiple genetic, environmental, and maternal factors may be contributory, we observed five post-marketing reports of limb abnormalities including missing hands and/or reduced forearms with minocycline use. This is concerning since the animal studies submitted with Solodyn™ demonstrated fetal skeletal malformations occurring in the offspring of rats and rabbits after maternal exposure to minocycline. In addition, the Pregnancy section of the Minocin® label, another minocycline product, currently states that spontaneous reports of limb reductions have been reported. This labeling change was based on three cases of limb deformations; the Pregnancy and Lactation Team (PLT) and DDRE were consulted on this issue and made recommendations (PLT consults on July 16, 2003 and October 6, 2003; DDRE consult on June 10, 2003 [NDA Nos. 50-445/S-022, 50-649/S-015, 50-444/S-038]). Thus, we

recommend adding similar language to the Pregnancy section of Solodyn™ label to reflect that limb reductions have been reported in the post-marketing setting with minocycline use during pregnancy. We also suggest incorporating this information to the labels of all other brand and generic minocycline products. Our recommendation is also consistent with current recommendations from PLT for this supplement, dated December 15, 2005 (NDA 50-808).

2. DRUG INFORMATION/LABELING¹

Solodyn™ is a modified release caplet formulation of minocycline, which is a semi-synthetic derivative of tetracycline. Solodyn caplets are seeking approval for the treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.

The relevant product label sections for events reviewed in this consult are:

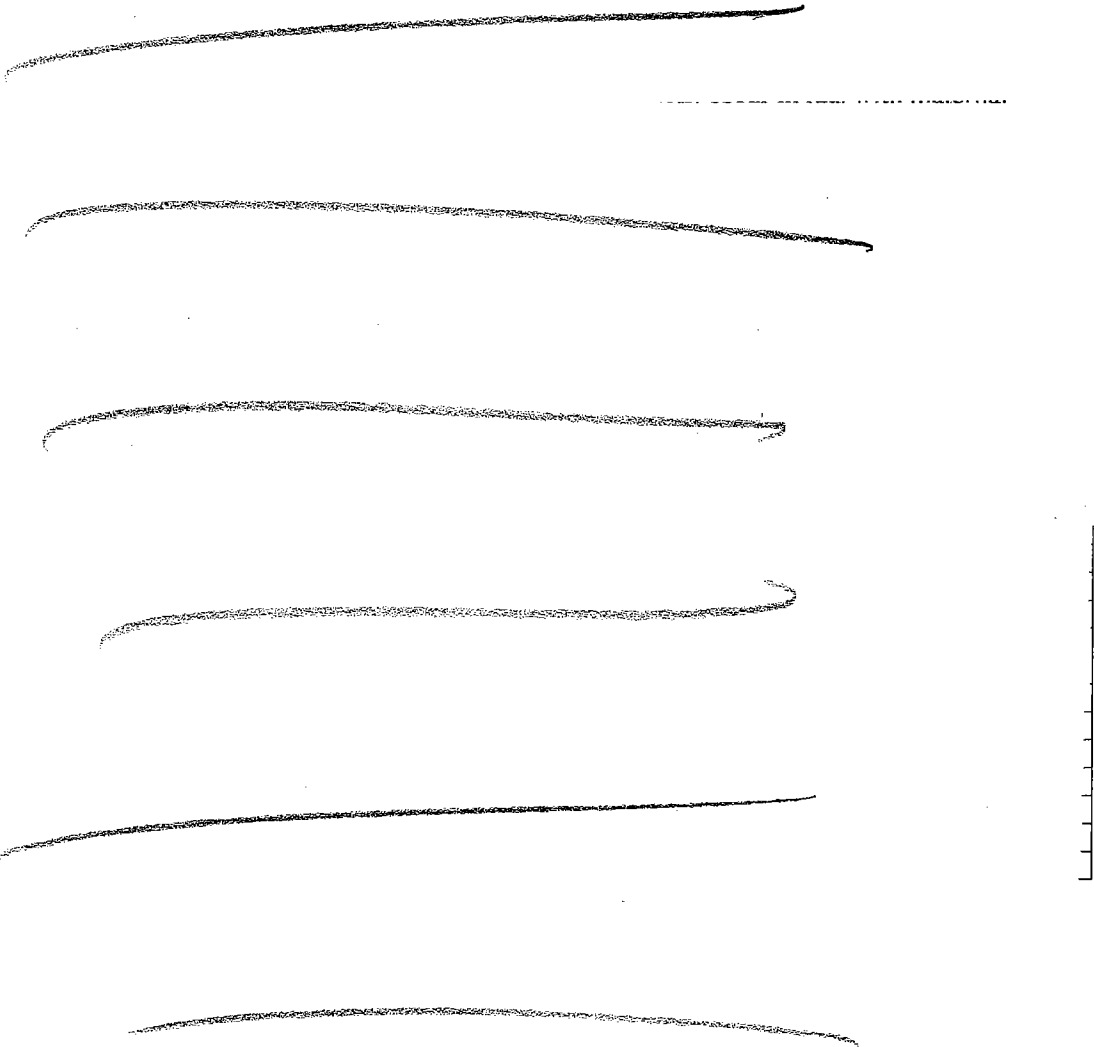
WARNINGS

MINOCYCLINE, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus.

PRECAUTIONS



3. SUMMARY OF DEATHS WITH ACNE INDICATION (N = 10)

An AERS search conducted on January 20, 2006 for death cases associated with minocycline use for acne resulted in 13 reports, representing 10 unique cases. The minocycline review from 2004 summarized six of these death cases. Since then, four additional post-marketing cases (US - 1, Foreign - 3) with death as an outcome have been reported and are described here. Three were reports of death from unknown causes that occurred after the patients experienced unspecified hepatic reactions after an unknown time following minocycline therapy. Information for these three cases was limited, since they were reported in a literature article summarizing hepatotoxicity cases associated with the use of minocycline in acne.² The last case of death represented a suicide with “diffusely black thyroid” upon autopsy.

The four new death cases since 2004 are summarized:

ISR#4360816-7, 2004, foreign²

A 17-year-old woman received minocycline for acne. Information about dates of minocycline therapy, dose regimen, her medical history, and concomitant medications were not provided. On an unknown date in 1998, she developed an **unspecified hepatic reaction** and died. The cause of death was not reported.

ISR#4360976-8, 2004, foreign²

A 20-year-old woman received minocycline for acne for 154 days (~5 months). On an unknown date in 1989, she developed an **unspecified hepatic reaction** and died. The cause of death was not reported.

ISR#4360398-X, 2004, foreign²

A 31-year-old man received one dose of 200mg minocycline for acne and developed an **unspecified hepatic reaction**. The time between the single dose of minocycline and the development of the hepatic reaction was not reported. On an unknown date, he died. No further information was available.

ISR#4459170-1, 4464784-9, US

A 19-year-old man received minocycline for acne. About two weeks later, he had episodes of rapid heart beat and shortness of breath for the first time; three months later, he received fluoxetine for these symptoms. Minocycline was not discontinued. When these symptoms worsened, fluoxetine dose was increased, and he showed improvement. However, about a year later, he shot himself. On autopsy, a “diffusely black thyroid” was noted.

4. SUMMARY OF LIVER INJURIES WITH ACNE INDICATION

Part I: Overview of all liver injury cases (n = 165)

An AERS search was conducted on January 20, 2006 for all liver injury cases associated with minocycline use for acne. The search was conducted using the ‘ODS Liver All’ case definition, which includes Hepatic and Hepatobiliary Disorders (HLGT), Hepatobiliary Investigations (HLGT), and Liver Transplant (PT).

The search identified 165 liver injury reports, of which 60 were US reports. The reports included 109 females and 54 males. Five reported an outcome of death, 89 reported hospitalization, and 9 reported the events as life-threatening. Of five death reports related to liver injury, one was a duplicate report.

The 10 most commonly reported adverse event PT terms are listed in the table below*:

Rank	Adverse event Preferred Terms (PT)	# of reports	Label status of Event
1	Liver Function Test Abnormal	46	Unlabeled ^a
2	Pyrexia	36	Labeled
3	Arthralgia	32	Labeled

3	Hepatitis	32	Labeled
4	Alanine Aminotransferase Increased	30	Labeled
5	Antinuclear Antibody Positive	29	Unlabeled ^b
6	Lymphadenopathy	26	Labeled
7	Aspartate Aminotransferase Increased	24	Labeled
8	Jaundice	22	Unlabeled ^a
9	Autoimmune Hepatitis	21	Unlabeled ^a

*Note: A report may contain more than one PT terms.

^aLabeled for increases in liver enzymes, hepatitis, and hepatic failure

^bLupus-like syndrome is labeled, for which the laboratory findings may include positive antinuclear antibody

Part II: Overview of liver failure/cirrhosis cases (n = 9)

Due to the volume of all liver injury cases and the need for a timely response, we concentrated our efforts on severe liver injuries, particularly liver failure cases. ODS Liver Failure/Cirrhosis search criteria was used; this is an ODS-defined grouping of terms related to Hepatic Failure and Associated Disorders (HLT; this includes PT terms of hepatic failure, hepatorenal failure, hepatic encephalopathy, hepatic coma, and asterixis), Hepatic Fibrosis and Cirrhosis (HLT; this includes PT terms of biliary cirrhosis, primary biliary cirrhosis, biliary fibrosis, alcoholic cirrhosis, hepatic cirrhosis, and hepatic fibrosis), Hepatic Necrosis (PT), Hepatitis Fulminant (PT), and Liver Transplant (PT).

This search identified 12 reports, representing nine unique cases of liver failure/cirrhosis associated with minocycline for acne indication. Of note, a death case from the 2004 review was included in this case series, as the death was due to acute fulminant hepatic failure. Six cases were literature reports.³⁻⁸ Seven hepatic events occurred in women and six were foreign reports. The patients' ages ranged from 12 to 49 years, with a median of 16 years. Six of nine cases reported hepatic failure. Four of six hepatic failure cases were associated with hypersensitivity syndrome and/or skin eruptions; one case was an autoimmune hepatitis that progressed to hepatic failure; and the last case was an unspecified acute hepatitis/hepatic failure. The remaining three liver injury cases included a case of autoimmune hepatitis with cirrhosis, granulomatous hepatitis, and an unspecified hepatitis with jaundice and encephalopathy. The time to event onset ranged from one week to seven years, with a median of one month. The majority of cases (n=6), however, experienced severe liver injury within one month of initiating minocycline. These early-onset hepatic events occurred in patients reporting granulomatous hepatitis, unspecified hepatitis, and four hepatic failure cases associated with skin eruptions and/or hypersensitivity. The remaining three patients, two autoimmune hepatitis cases and an unspecified hepatic failure case, reported a longer time to event onset of one year or longer.

Some of the common presenting signs and symptoms included fever (4), skin rash (5), and jaundice (3). Other hypersensitivity-like findings such as eosinophilia (3) and increased IgE levels (2) were also reported. Transaminase elevations ranged from 3- to 50-fold above normal. Two patients also experienced concurrent renal failure along with liver failure as part of their hypersensitivity reaction; acute interstitial nephritis was observed in their kidney biopsies. Two patients reported positive antinuclear antibodies (ANA); one of these patients also reported positive anti-dsDNA, anti-smooth muscle, and anti-skeletal muscle antibodies. A liver biopsy from a patient showed chronic hepatitis developing into cirrhosis, despite having no previous medical history of hepatitis. A skin biopsy in one patient showed leukocytoclastic vasculitis. One patient, with an outcome of death, also received erythromycin for five days before the symptoms progressed; however, the signs/symptoms began during minocycline therapy.

One pediatric patient died due to fulminant hepatic failure. Another patient required emergent liver transplantation for recovery. Four other patients recovered from hepatic events after minocycline was discontinued, with three patients requiring corticosteroid therapies. One patient did not recover from the liver injury. The outcome of the liver injuries in the remaining two patients was not reported.

A representative case is summarized:

ISR#3484432-4, 2000, foreign⁷

A 20-year-old woman received minocycline for about three years for treatment of acne vulgaris. She was hospitalized with 'mild' jaundice, pruritus, and abnormal liver function tests after a gastrointestinal infection. She refused further evaluation and was discharged. Several weeks later, she was re-hospitalized with jaundice and a 5-kilogram weight loss over two months. Laboratory tests showed increased liver enzymes (ALT 199 IU/L, AST 266 IU/L, GGT 34 IU/L, Alkaline phosphatase 332 IU/L, bilirubin 11.7 mg/dL) and elevated IgE (1320 IU/mL). A liver biopsy showed "histological features of necrotizing hepatitis." The ANA, anti-dsDNA, anti-smooth muscle, and anti-skeletal muscle antibodies were all positive. A diagnosis of autoimmune hepatitis was assumed. The patient's condition worsened to include fulminant hepatic failure and coma. The patient was placed on a liver transplant list as "highly urgent" and transplant was performed the same day. Follow-up laboratory performed a couple of months later showed resolution of all abnormalities except GGT (64 IU/L), alkaline phosphatase (171 IU/L), IgE (349 IU/mL), and positive ANA. The patient recovered without further complications.

5. SUMMARY OF LUPUS EVENTS WITH ACNE INDICATION

Part I: Overview of all lupus cases (N = 66)

An AERS search was conducted on January 20, 2006 for all lupus cases associated with minocycline use for acne. This search used two HLTs: 1) Lupus Erythematosus (incl subtypes) and 2) Lupus Erythematosus and Associated Conditions. The search resulted in 66 lupus reports, of which 30 were US reports. The reports included 54 females and 10 males. Two reports did not provide gender information. Eighteen reported hospitalization, and two reported the events as life-threatening. Neither death nor congenital anomaly was reported with lupus.

The 10 most commonly reported adverse event PT terms are listed in the table below*:

Rank	Adverse event Preferred Terms (PT)	# of reports	Label Status of Event
1	Systemic lupus erythematosus	34	Unlabeled ^c
2	Lupus-like syndrome	29	Labeled
3	Arthralgia	19	Labeled
4	Antinuclear antibody positive	15	Unlabeled ^b
5	Pyrexia	10	Labeled
6	Liver function test abnormal	9	Unlabeled ^a
7	Arthritis	8	Unlabeled
8	Red blood cell sedimentation rate increased	7	Unlabeled
9	Autoimmune hepatitis	6	Unlabeled ^a
9	Hepatitis	6	Labeled

*Note: A report may contain more than one PT terms.

^aLabeled for increases in liver enzymes, hepatitis, and hepatic failure

^bLupus-like syndrome is labeled, for which the laboratory findings may include positive antinuclear antibody

^cLabeled for exacerbation of systemic lupus

Part II: Overview of lupus cases with outcomes of death, hospitalization, and life-threatening (N = 18)

The search for lupus/lupus-like syndrome cases associated with minocycline use for acne with outcomes of death, hospitalization, and life-threatening identified 19 reports, representing 18 unique cases. The majority of cases occurred in females (n=16) and the majority were foreign reports (n=13). Five of 18 cases were literature reports.⁹⁻¹³ The patients' ages ranged from 14 to 42 years, with a median of 19 years (n=17). The time to event onset ranged from two months to five years, with a median of 2 years (n=11). [Note: Some patients used minocycline intermittently for acne flare, and the time to onset was calculated from the first exposure to minocycline.]

Most patients presented with constitutional and musculoskeletal symptoms such as polyarthritis/arthralgia (12), fever (5), and/or rash (3). One patient experienced pulmonary lupus¹⁰, and another patient experienced interstitial pneumonia along with lupus. Liver involvement with lupus was reported in six

patients – five patients had concurrent autoimmune hepatitis, and one patient reported elevated liver enzymes. In two patients, lupus was preceded by polyarthritis/arthritis. The antinuclear antibodies were positive in 11 patients; the antineutrophil cytoplasmic antibodies (ANCA) were positive in four patients (three specified positivity to perinuclear, or p-ANCA). Other significant findings included positive anti-dsDNA antibodies (1), anti-smooth muscle antibodies (1), and the presence of circulating immune complex (1). Past medical history was significant in one patient with a history of Hashimoto's thyroiditis. No patients reported using concomitant drugs that have been linked to lupus in the literature¹⁴.

Seventeen patients were hospitalized and two patients considered the event to be life-threatening. Eleven patients received therapy for lupus, including corticosteroids (8), NSAIDS (5), hydroxychloroquine (1), and an unspecified immunosuppressant (1). Treatment with NSAIDS was ineffective in three of five patients; in two of these patients, subsequent therapy with corticosteroids proved to be effective. Eleven patients (61%) reported recovery or improvement following discontinuation of minocycline. In one patient, minocycline therapy was restarted and lupus syndrome recurred; the reaction abated again when minocycline was discontinued. Four patients did not recover despite discontinuation of minocycline. The outcome in the remaining two patients was not reported.

A representative case is summarized:

ISR#3301713-5, 1999, US¹⁰

A 16-year-old woman received minocycline for acne for more than two years. Concomitant therapy included thyroxine and azithromycin. Her medical history was significant for Hashimoto's thyroiditis. She presented to the hospital with progressive dyspnea, severe cough, and coughing paroxysms. She had also been suffering from joint pain with swelling and stiffness, fevers, generalized weakness, and a 9-kilogram weight loss. On physical exam, she had fever and lung auscultation showed diffuse crackles. The laboratory tests showed elevated liver enzymes (AST 253 IU/L, ALT 479 IU/L), elevated ESR, positive ANA of 1:160, positive antihistone antibodies of 3.4, positive anti-dsDNA antibodies of 345 U/mL, and positive c-ANCA of 1:640 and p-ANCA of 1:80. A chest X-ray showed bilateral pulmonary infiltrates with small pleural effusion. The pulmonary function tests showed significant restrictive lung disease. Minocycline was discontinued. The patient received intravenous methylprednisolone for three days and was switched to oral prednisone. Upon treatment the patient demonstrated dramatic clinical, laboratory, and radiographic improvement. Follow-up pulmonary function tests a month after discharge were normal indicating reversible lung disease, with laboratory values returning to normal at 6 months of follow-up.

6. SUMMARY OF SKIN/PHOTOSENSITIVITY EVENTS WITH ACNE INDICATION (N=16)

An AERS search was conducted on January 20, 2006 for skin adverse events and photosensitivity reactions associated with minocycline use for acne. The search for skin adverse event reports was conducted using the 'ODS Serious Skin' case definition, which includes Bullous Conditions (HLT) and

Acute Generalized Exanthematous Pustulosis (PT). In addition, the term Photosensitivity Conditions (HLT) was used to search for reports of photosensitivity reactions. The search resulted in 17 cases of skin/photosensitivity reactions; one case was neither a skin nor a photosensitivity reaction and thus was excluded from further review. It should be noted that three cases from other sections were included in this case series. First was the 'hypersensitivity myocarditis' death case from the 2004 review, as she experienced Stevens Johnson syndrome during minocycline therapy prior to events related to her death. Second was a case of liver failure (from section 4, part II) since the patient experienced pustular rash along with liver failure. Lastly, a lupus case (from section 5, part II) reported a constellation of symptoms including photosensitivity during 26 years of minocycline use.

Of 16 included cases of skin eruptions, rashes in four cases were reported to be photosensitivity reactions. Twelve cases were female, and nine were foreign reports. One was a literature report.¹⁵ The patients' ages ranged from 15 to 65 years, with a median of 22 years (n=15). The reported skin eruptions not due to photosensitivity reactions included Stevens Johnson syndrome (3), erythema multiforme (4), bullous dermatitis/rash (4), and pustular rash (1). The time to event onset ranged from two days to three months, with a median of 23 days (n=12). Eight cases reported hospitalization, and two cases reported disability due to skin reactions after minocycline use. One patient with erythema multiforme reported previous use of minocycline about a year ago without any skin reactions. Erythema multiforme in one patient was part of presenting symptoms of her serum sickness. The rash in a case of photosensitivity reaction manifested as part of a hypersensitivity reaction with acute respiratory distress syndrome.¹⁷ The patient's rash progressed to severe erythematous skin rash in all sun-exposed area after three weeks of continued use of minocycline, along with peripheral eosinophilia, severe hypoxemia, and extensive lung infiltrates. This patient received steroids, antibiotics, and required mechanical ventilation; her symptoms eventually disappeared.

Eight patients recovered from the skin reactions, including the above mentioned photosensitivity case. However, two patients with bullous dermatitis did not recover from the event, with one patient requiring skin grafting on legs due to progressive, necrotic bullous degenerative lesions. In one case of photosensitivity reaction, symptoms of rash persisted despite discontinuation of minocycline, which required continued corticosteroid therapy. The outcomes in five remaining cases were not reported. One patient experienced recurrence of erythema multiforme upon re-exposure to minocycline; the event again abated upon discontinuation of minocycline therapy.

A representative case is summarized:

ISR#3388691-8, 1999, foreign

A 65 year old woman received minocycline 50mg twice daily for 11 days for acne therapy. Concomitant therapy included propylthiouracil, fenofibrate, spironolactone, triazolam, and metronidazole topical gel. Ten days after starting minocycline, she had fever, leucopenia, and "major inflammatory syndrome". A day later, she experienced ecchymosis, initially at a few sites then progressing to all four limbs within a few hours. Necrotic bullous degenerative lesions appeared on the face, legs, and forearms. She was transferred to a burn center and skin grafting was performed on her legs. At the time of report, the patient was to be discharged in a few days.

7. SUMMARY OF ANAPHYLACTIC REACTIONS (N=6)

An AERS search was conducted for reports of anaphylactic reactions associated with minocycline use for acne. The search was conducted using Anaphylactic Responses (HLT). The search identified six reports, of which three were US reports and three cases occurred in females. The patients' ages ranged from 15 to 50 years, with a median of 29 years. Three patients reported history of allergy to penicillin, cephalosporins, or tetracycline. One patient reported using a different brand of minocycline "for years" without any problem, but he experienced anaphylaxis after initiating therapy with this particular brand.

All except one case reported experiencing anaphylaxis or anaphylactoid reaction after ingesting one dose or on the same day of initiating minocycline treatment. One case reported longer time to onset of ten days; this patient reported previous tetracycline allergy. This case was also unusual in that discontinuation of minocycline and therapy with corticosteroid did not completely improve his signs/symptoms. In fact, four days later, after completing corticosteroid therapy, he was hospitalized due to breathing difficulty and throat swelling. The patient's eventual outcome was not reported. Although this represents a unique case and may not represent anaphylactic event due to minocycline, the patient did not report receiving any other medications.

Three patients visited the emergency room. Serious outcomes were reported in all six cases; the event was life-threatening in two cases, resulted in hospitalization in two cases, and both life-threatening and hospitalization were reported in the remaining two cases. Four patients reported recovery, and the outcomes in the remaining two cases were unknown.

A representative case is summarized:

ISR#3749150-3, 2001, US

A 15-year-old male adolescent received minocycline for acne. His past medical history was significant for asthma and penicillin allergy. He was also receiving Proventil inhaler. Within 15 minutes of first minocycline dose, the patient experienced an anaphylactic reaction consisting of "intense" itching, facial

redness, face/neck swelling, and respiratory distress. He was taken to the emergency room, and recovered following intervention. The event was considered life-threatening.

8. SUMMARY OF CONGENITAL ANOMALY FOR ALL MINOCYCLINE INDICATION (N = 21)

An AERS search was conducted on January 20, 2006 for reports of congenital anomaly associated with minocycline use, regardless of its indication. The search used two SOCs: 1) Pregnancy, Puerperium and Perinatal Conditions and 2) Congenital, Familial and Genetic Disorders. In addition, a search was performed using 'congenital anomaly' as an outcome. The search identified 31 reports, of which two were duplicates and eight did not report congenital anomaly. Therefore, we included 21 cases in our final review.

Of 21 congenital anomaly cases, all except one were foreign reports. One was a literature report.¹⁶ All exposures were maternal, except one where possible exposure occurred through the father's use of minocycline. The mothers' ages at the time of pregnancy ranged from 15 to 38 years, with a median of 30 years (n=10). The indication for minocycline included acne (9), pelvic inflammatory disease (2), lower respiratory tract infection (1), and cutaneous allergy (1). Fourteen women reported minocycline exposure around the time of conception and/or during their first trimester of pregnancy; one woman reported exposure during her second trimester; one possible paternal exposure occurred around the time of conception; and the drug exposure information was not provided in the remaining five patients. Two women reported no previous pregnancies and one woman reported previous delivery of a healthy child. Five women reported using concomitant pregnancy category D/X drugs, including benzodiazepines (2), tetracycline (1), doxycycline (1), and norethindrone (1).

Five women chose to have elective abortions after discovering congenital anomalies in the fetuses; these anomalies included urogenital defect, cystic hygroma, asymmetrical intrauterine growth retardation/triploidy, left heart hypoplasia, and an unspecified musculoskeletal malformation. One patient miscarried a few weeks after discovering an absent fetal heart. Fifteen cases resulting in delivery described the following congenital anomalies (including one possible paternal exposure case):

Infant #	Description of congenital anomalies
1	No right hand
2	Partial left forearm and absent left hand
3	Limb reduction of left forearm possessing rudimentary digits
4	No left hand and part of forearm
5	Dysmorphic features including abnormal face and ears, absent right hand, four fingers of left hand, abnormal toenails, sacral pit, Fallot's tetralogy with trisomy 6, growth

	retardation
6	Congenital positional talipes
7	Bilateral non varus equines talipes
8	Right renal hypoplasia and compensated left kidney hyperplasia
9	Right testis teratoma and left testis ectopy
10	Dorsolateral diaphragmatic hernia
11	Ventricular septal defect
12	Anophthalmia, esophageal atresia
13	Microcephaly, absent palate, huge harelip, undeveloped nose, close-set eyes
14	Undefined congenital anomaly
15*	Cleft palate and ankyloblepharon filiforme

*Possible paternal exposure

Five infants (#1-5) reported some sort of limb abnormalities including missing hands and/or reduced forearms. Three infants (#5, 12, 13) had abnormalities involving facial structure, and two infants had talipes at birth. The infant (#5) with dysmorphic features, limb abnormality, Fallot's tetralogy, etc showed abnormal karyotype; however, the parents had normal karyotypes.

Two woman reported potential environmental/occupational exposure that may have played a role in the reported congenital anomalies. The mother who gave birth to the infant with triploidy was a nurse and had exposures to X-rays. In addition, the mother of the infant with anophthalmia and esophageal atresia worked as a cleaner and handled a variety of dishwashing and cleaning products; however, according to the reporter, this was considered to be a sporadic case and not attributed to minocycline therapy. Two infants died (#5, 12) within one week of delivery.

9. DISCUSSION

As of January 20, 2006, the AERS database contained 4795 adverse event reports associated with minocycline use, of which 733 were reports of adverse events in acne. Since DDRE performed a comprehensive review of minocycline dated April 21, 2004 (NDA No. ~~150-445~~/50-445/50-451/50-649/50-315. ~~50-444~~), this consult will focus on reports of death, liver injuries, lupus, skin/photosensitivity reactions, and congenital anomaly as specified by the requesting medical officer. In addition, we independently reviewed reports of anaphylactic reactions. DDRE and DDDP agreed to limit the review to reports of minocycline use for acne, except for the congenital anomaly cases, where we reviewed all reported cases.

The 2004 review of minocycline summarized six death cases. Since then, four additional post-marketing cases reported death as an outcome in patients who received minocycline to treat acne. Three deaths

occurred from unknown causes after the patients experienced unspecified hepatic reactions, and one was a suicide case.

Due to the volume of all liver injury reports and the need for a timely response, we concentrated our efforts on severe liver injuries, particularly liver failure cases. The AERS database contained 165 liver injury reports associated with minocycline use for acne; of these, nine unique cases were identified as severe liver injuries based on ODS Liver failure/cirrhosis search criteria (see section 4, Part II for description of this criteria). Six of nine cases reported hepatic failures. Four of six hepatic failure cases were associated with hypersensitivity syndrome and/or skin eruptions; one was an autoimmune hepatitis case that progressed to hepatic failure; and the last case was an unspecified acute hepatitis/hepatic failure. The remaining three liver injury cases included a case of autoimmune hepatitis with cirrhosis, granulomatous hepatitis, and an unspecified hepatitis with jaundice and encephalopathy. One pediatric patient died due to fulminant hepatic failure; another patient required emergent liver transplantation for recovery; and four other patients recovered.

Consistent with a literature review², we observed two patterns of hepatotoxicity with minocycline use in acne in our cases: 1) hypersensitivity reaction with a rapid onset of within one month of treatment, and 2) autoimmune hepatitis with a late onset of about a year or more therapy. The majority of our post-marketing cases (n=6) experienced severe liver injury within a month of minocycline therapy and were accompanied by skin eruptions and/or hypersensitivity-type of reaction.

We reviewed 18 post-marketing cases of lupus/lupus-like syndrome that reported death, hospitalization, and life-threatening outcomes. Most occurred in females and the time to onset ranged from two months to five years of minocycline therapy (median 24 months). Most patients presented with constitutional and musculoskeletal symptoms such as polyarthritis/arthralgia, fever, and/or rash. Concurrent liver involvement was reported in six patients (five had autoimmune hepatitis), and one patient experienced pulmonary lupus. The antinuclear antibodies were positive in 11 patients. The majority, 61% of patients, reported recovery or improvement following discontinuation of minocycline. One patient reported positive rechallenge.

Sixteen cases of skin eruptions, including four cases of rash due to photosensitivity reactions, were reviewed. The reports of skin eruptions not due to photosensitivity reactions included Stevens Johnson syndrome (3), erythema multiforme (4), bullous dermatitis/rash (4), and pustular rash (1). Eight patients recovered from the skin reactions, including one photosensitivity reaction case. However, two patients

with bullous dermatitis did not recover from the event, with one patient requiring skin grafting on legs due to progressive, necrotic bullous degenerative lesions. One patient with erythema multiforme reported positive rechallenge.

We reviewed six cases of anaphylactic reactions reported with minocycline use for acne. Most occurred within one dose or the same day of initiating minocycline therapy. Serious outcomes were reported in all six cases; the event was life-threatening in two cases, resulted in hospitalization in two cases, and both life-threatening and hospitalization were reported in the remaining two cases. Four patients recovered and the outcomes in the remaining two patients were unknown.

Minocycline is labeled as pregnancy category D and its use is not recommended during pregnancy. The concern with the use of minocycline during pregnancy, as a tetracycline-class antibiotic, has been the effect on fetal tooth and skeletal development, which is reflected in the labeling. We reviewed 21 post-marketing congenital anomaly cases. Fourteen women reported minocycline use around the time of conception and/or during their first trimester of pregnancy, and one patient reported drug use during her second trimester. One case of possible paternal exposure occurred during the time of conception. The time of minocycline exposure in the five remaining cases was not reported. Some confounders were present: five women reported using concomitant drugs that are labeled pregnancy category D/X and two women reported potential environmental/occupational exposure. Five women chose to have elective abortions after discovering congenital anomaly in the fetus; and another woman miscarried a few weeks after discovering an absent fetal heart. Fifteen congenital anomalies (one possibly due to paternal exposure) were reported with live births, with five live births reporting limb abnormalities including missing hands and/or reduced forearms. Two infants died within one week of delivery.

10. RECOMMENDATION

We summarized reports of death, liver injuries, lupus, skin/photosensitivity, and anaphylactic reactions with the use of minocycline for acne. The proposed label for Solodyn™ contains language regarding adverse events related to liver, lupus, serious skin reactions, and photosensitivity. The Precautions section states that _____, and the Adverse Reactions Section listed “hepatitis, liver failure.” Of 165 total liver injury reports (note: raw number, may contain duplicates) associated with minocycline use for acne, we reviewed nine unique cases of severe liver injuries, which included six liver failure cases. In our case series, one patient died due to fulminant hepatic failure; three

patients reported death after experiencing unspecified hepatic reactions; one patient required an emergent liver transplant; another patient with acute hepatitis/liver failure did not recover; and four patients with lupus (two of whom also exhibited autoimmune hepatitis/hepatitis) did not recover from the adverse event. Given these reports of serious liver injury reactions in patients treated for acne, we recommend that a "Hepatotoxicity" section be placed in the Warnings of the label to inform prescribing practitioners that serious liver injury cases, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal), have been observed in the post-marketing setting. We also suggest adding autoimmune hepatitis to the label.

Our review of skin eruptions included severe cutaneous reactions - three cases of Stevens Johnson syndrome (SJS), four cases of erythema multiforme (EM), and four cases of bullous dermatitis/rash. One patient with bullous dermatitis required skin grafting due to progressive, necrotic lesions. In addition, we reviewed six cases of anaphylactic reactions, which represent a severe and life-threatening form of drug hypersensitivity; four of these were considered life-threatening. Based on these cases, we recommend adding a "Serious Skin/Hypersensitivity Reaction" section under Precautions, to inform prescribing practitioners that post-marketing cases of anaphylaxis and serious skin reactions (such as SJS and EM) have been reported. We concur with the current label information concerning lupus, and make no further recommendations based on our current review of post-marketing lupus cases reported with minocycline use for acne.

Lastly, all congenital anomaly reports associated with minocycline, regardless of its indication, were reviewed. The label advises against its use during pregnancy, with warnings about the effect on fetal tooth and bone. Although it is often difficult to determine specific causality for birth defects since multiple genetic, environmental, and maternal factors may be contributory, we observed five post-marketing reports of limb abnormalities including missing hands and/or reduced forearms with minocycline use. This is concerning since the animal studies submitted with Solodyn™ demonstrated fetal skeletal malformations occurring in the offspring of rats and rabbits after maternal exposure to minocycline. In addition, the Pregnancy section of the Minocin® label, another minocycline product, currently states that spontaneous reports of limb reductions have been reported. This labeling change was based on three cases of limb deformations; the Pregnancy and Lactation Team (PLT) and DDRE were consulted on this issue and made recommendations (PLT consults on July 16, 2003 and October 6, 2003; DDRE consult on June 10, 2003 [NDA Nos. 50-445/S-022, 50-649/S-015, 50-444/S-038]). Thus, we recommend adding similar language to the Pregnancy section of Solodyn™ label to reflect that limb reductions have been reported in the post-marketing setting with minocycline use during pregnancy. We

also suggest incorporating this information to the labels of all other brand and generic minocycline products. Our recommendation is also consistent with current recommendations from PLT for this supplement, dated December 15, 2005 (NDA 50-808).

11. REFERENCES

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Hyon J. Kwon, Pharm.D., M.P.H.

Concur:

Marilyn R. Pitts, Pharm.D., Team Leader

cc:

NDA 50-808

DDDP Kukich/Luke/Nikhar/Curtis/Division File

DDRE Avigan/Johann-Liang/Pitts/Beam/Division File

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Hyon Kwon
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DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
3/16/2006 02:24:51 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: March 10, 2006 @ 1:30 P.M.

APPLICATION NUMBER: NDA 50-808

DRUG PRODUCT: Solodyn (Minocycline Hydrochloride)

BETWEEN:

Division of Dermatologic and Dental Drug Products, HFD-540

Markham Luke, M.D./Clinical Team Leader, DDDP, HFD-540

Felecia Curtis, Regulatory Project Manager

AND

Attendees via teleconference:

R. Todd Plott, M.D., Vice President, Clinical Research and Regulatory Affairs

Michelle Wells, Regulatory Affairs Consultant for Medicis

SUBJECT: NDA 50-808

This teleconference was initiated by the Agency to request information from Medicis Pharmaceutical for NDA 50-808.

The Agency requested that the sponsor submit a patient package insert (PPI) for review.

The sponsor agreed to submit information requested in timely manner to expedite the review process.

The conversation ended amicably.

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/s/

Felicia Curtis
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Markham Luke
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MEDICAL OFFICER



March 14, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Response to FDA Request for Information

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets)
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended-Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the FDA faxed filing communication dated January 31, 2006, received on March 10, 2006, requesting information pertaining to chemistry, manufacturing and controls sections of the NDA.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

Enclosed please find a detailed summary including FDA's comments in bold italics followed by Medicis' responses to the January 31, 2006 fax.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fw/dms



March 14, 2006

Caryn McNab
DHHS/FDA/ORAP-FO/LOS-DO
ATTN: Drug Preapproval Manager
Mail stop HFR-PA250
19701 Fairchild
Irvine, CA 92612-2506

Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets)
45 mg, 90 mg and 135 mg

Dear Ms. McNab:

A field review copy of Medicis' March 14, 2006 response to FDA's January 31, 2006 CMC Information Request for NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets) is enclosed.

I hereby certify that the enclosed documentation is a true copy of the archival and review copies of the response to FDA's January 31, 2006 CMC Information Request for NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets) submitted to FDA headquarters in Rockville, MD.

This certification is provided in accordance with 21 CFR 314.50(l)(3).

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Todd Plott".

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

fww/dms

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): .Mail: Nancy Clark, DSRCS HFD-410		FROM: Felecia Curtis//Derm and Dental 60877		
DATE March 13, 2006	IND NO.	NDA NO. 50-808	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT
NAME OF DRUG Solodyn (Minocycline Hydrochloride)		PRIORITY CONSIDERATION March 17, 2006	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 3/17/2006
NAME OF FIRM: Medicis				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): PPI/Medication Guide				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: COMMENTS / SPECIAL INSTRUCTIONS: Attached is the electronic copy. PDUFA DATE: 5/8/06 CC: Archival IND/NDA 50-808 HFD-540/Division File HFD-540/Felecia Curtis HFD-540/Reviewers and Team Leaders				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

3 Page(s) Withheld

 Trade Secret / Confidential

 2 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-_____

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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
3/13/2006 09:13:15 AM



March 10, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets)
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended-Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to today's phone contact between Medicis representatives, Dr. Todd Plott and Michelle Wells, and FDA representatives, Felecia Curtis and Dr. Markham Luke during which a request for a Patient Package Insert was made.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Request with regard to the pending New Drug Application (NDA) 50-808.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

**Appears This Way
On Original**



March 3, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Labeling Amendment

**Re: NDA 50-808 SOLODYN™ (minocycline hydrochloride, USP, extended-release tablets)
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ Extended-Release Tablets, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the March 1, 2006 FDA faxed filing communication, requesting revisions to the drug product's labeling.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the FDA Labeling Request with regard to the pending New Drug Application (NDA) 50-808.

The enclosed labeling has been revised in accordance with the Agency's comments. A detailed summary of the labeling changes is enclosed. The Word package insert is also enclosed to facilitate review.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

dms

**Appears This Way
On Original**



March 1, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Response to FDA
Request for Information**

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride, USP, extended-release tablets)
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ (Minocycline Hydrochloride) Extended-Release 45 mg, 90 mg and 135 mg, submitted on June 30, 2005 and to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the February 28, 2006 telephone contact between Medicis and Felecia Curtis (FDA) in which FDA questioned if Medicis would be submitting a patient package insert for SOLODYN™ Extended-Release Caplets.

Medicis did not include a separate patient package insert in this NDA because line 169 of the package insert filed on February 10, 2006, includes the following instructions for patients:

Information for Patients

SOLODYN™ Extended-Release Caplets

Should you have questions or need additional information, please do not hesitate to contact _____, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corporation

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

dms

FDA Fax Memo

Date: March 1, 2006

Subject: **NDA 50-808 CMC & Clinical IR**

Hi Michele,

We are reviewing the Chemistry and Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We noted your response to our partial comments in 2/15/06 submission. Both FDA's comment and your response are listed below:

COMMENT

The proposed establish name is (Minocycline Hydrochloride) Modified Release . For modified release USP recognizes either extended release or delayed release. Based on the proposed formulation and release rate, the dosage form is extended release product. As a dosage form, USP recognizes tablet dosage form; therefore, include caplet in the package insert. Since tablet strength is for minocycline, include minocycline in the package insert. Thus the establish name of the drug product is (Minocycline Extended -release Tablet). Please explain if there is any concern for this recommendation.

RESPONSE

Medicis accepts the agency's recommendation for the proposed established name "Minocycline Extended-Release Tablets". Also as recommended by the agency, the labeling will reflect the active ingredient minocycline hydrochloride and the caplet dosage form as follows: "Minocycline Hydrochloride Extended-Release ".

Please note that upon further consultation with our Labeling and Nomenclature Committee, the recommendations are:

- (1). The establishment name format: (minocycline hydrochloride, USP, extended-release tablets)
- (2). delete the word caplet and replace with tablet throughout the package insert, and on container, carton, and blister labels. Please let me know if there is any concern.

The Clinical reviewer requests the following information for the label:

- For AE tables in the Solodyn label please provide two groups
 - 1) AEs in 5% or more of subjects
 - 2) AEs in 1% or more of subjects
- AEs in < 1% of subjects need not be included in the tabular form, but can be described as 'Other AEs in < 1% of the population included ...'
- For both please provide minocycline and placebo AEs in number and in brackets percentage i.e. N (%).

Please submit this information by 12 noon on March 3, 2006. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Respectfully,
Felecia Curtis

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

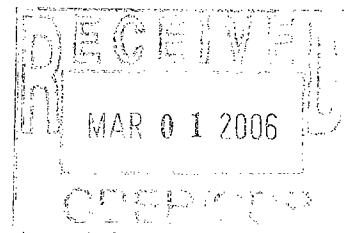
/s/

Felicia Curtis
3/1/2006 12:22:45 PM
CSO



RECEIVED

MAR - 3 2006



February 28, 2006

CDER White Oak DR1

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

DUPLICATE

NEW CORRESP

N 000 C

Notice of Withdrawal

Re: **NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release**
45 mg, 90 mg and 135 mg

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ (Minocycline Hydrochloride) Extended-Release
45 mg, 90 mg and 135 mg, submitted on June 30, 2005 and to IND 65,398 submitted on
July 12, 2002 in support of this NDA.

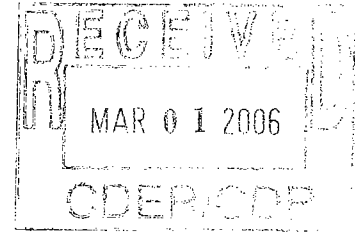
Reference is also made to Medicis' February 17, 2006 CMC Amendment which included the
proposed addition of _____ as an alternative outside laboratory, and to the February
27 and 28, 2006 contacts between Medicis and Felecia Curtis (FDA) in which Medicis was notified
the addition of _____ could trigger a cGMP inspection and ultimately extend the NDA's
PDUFA date.

However, at the request of the Division, Medicis hereby withdraws the addition of: _____
without prejudice to future refiling. Medicis intends to refile this information as a Special Supplement
- Changes Being Effected in 30 Days.

Should you have questions or need additional information, please do not hesitate to contact Michelle
Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corporation



February 28, 2006

Caryn McNab
DHHS/FDA/ORA/P-FO/LOS-DO
ATTN: Drug Preapproval Manager
Mail stop HFR-PA250
19701 Fairchild
Irvine, CA 92612-2506

Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release ~~_____~~
45 mg, 90 mg and 135 mg

Dear Ms. McNab:

A field review copy of the February 28, 2006 Notice of Withdrawal to NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release ~~_____~~ is enclosed.

I hereby certify that the enclosed documentation is a true copy of the archival and review copies of the Notice of Withdrawal to NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release ~~_____~~ submitted to FDA headquarters in Rockville, MD.

This certification is provided in accordance with 21 CFR 314.50(l)(3).

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

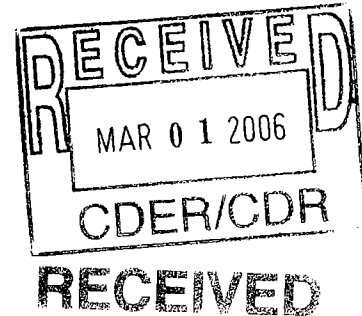
dms



ORIG AMENDMENT

N-060-BP

DUPLICATE



MAR - 3 2006

CDER White Oak DR1

Pharmacology/Toxicology Response

February 28, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____ 45 mg, 90 mg and 135 mg, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Further reference is made to the Information Request Letter dated February 27, 2006, requesting Pharmacology/Toxicology information. The following information is provided as a formal, written response:

- The sponsor acknowledges that the outlines of carcinogenicity study protocols contained within the referenced applications are not adequate to permit evaluation of the appropriateness of the proposed carcinogenicity studies.
- As a Phase IV condition of approval, Medicis commits to evaluate the carcinogenicity of Minocycline HCl.
- Upon approval of the NDA, carcinogenicity studies required in accordance with 21 CFR 214.50(d)(2)(ii) will be submitted per the "Guidance for Industry - Carcinogenicity Study Protocol Submissions."

Medicis has previously provided final reports for the 90-day rat study (VTK005) and 90-day mouse study (VTK006) as part of submission S-0023 dated January 7, 2005 as well as a paper outlining dose-justification as part of submission S-0038 dated August 12, 2005. This information, along with the draft protocols, will be the basis of the information Medicis will provide to the Division and the Executive Carcinogenicity Assessment Committee to evaluate the design of the studies. Medicis looks forward to an iterative process with the Division and Executive Carcinogenicity Assessment Committee to ensure that the study design and dose selection of these studies fulfills the Agency's requirements.

NDA 50-808
SOLODYN™ (Minocycline Hydrochloride) Extended-Release
45 mg, 90 mg and 135 mg
Response to FDA's February 27, 2006 Information Request

Medicis Pharmaceutical Corporation
February 28, 2006

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corporation

Appears This Way
On Original

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Tuesday, February 28, 2006 5:34 PM
To: Michelle Wells; Curtis, Felecia
Subject: RE: NDA 50-808

Attachments: cover.pdf; field cert.pdf; 356h.pdf; emfalert.txt



cover.pdf (50 KB)



field cert.pdf (40 KB)



356h.pdf (172 KB)



emfalert.txt (2 KB)

Now I have attached the letter withdrawing

{ ~~_____~~
alternate testing labs.

Since I am sending these to you electronically, and they are cover letters only, I did not send paper copies to your desk but can do so if you need them.

Thanks again for your guidance and help. Still working on the PPI letter. (Wasn't sure if you'll send a fax for the PPI letter.)

Michelle

-----Original Message-----

From: Michelle Wells
Sent: Tuesday, February 28, 2006 3:24 PM
To: Curtis, Felecia (E-mail)
Subject: NDA 50-808

Felecia -

Here's the Pharm/Tox Info Request response. Thanks for your help understanding the necessary commitments to make in the letter - I hope this meets your needs.

We are still working on 1) a letter indicating that we did not file a PPI, and 2) a letter withdrawing _____ as an alternate testing lab. I am still hoping to e-mail them to you tonight, or first thing in the morning at the latest.

We have/will make all these submissions electronic (PDF cover letters and forms) to the EDR at the Ammendale address.

ease don't hesitate to contact me with questions.

Regards,
Michelle

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800
Direct: 602 808 3851
Fax: 602 778 6051
Cell: 480 221 9968

wells@medicis.com <<mailto:mwells@medicis.com>>



February 22, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Response to FDA Request for
Information**

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended Release Tablets
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™, previously referred to as Modified Release — now referred to as Extended Release Tablets submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the February 21, 2006 FDA faxed filing communication, providing a request for Clinical and Pharmacology/Toxicology information submitted in the NDA filing for this product.

Below please find FDA's comments in *italics* followed by Medicis' responses to the February 21, 2006 FDA fax.

FDA Comment 1:

In the Solodyn label, please include the placebo group for comparison purposes in the tabulated list of adverse events for the <5% group.

Medicis response:

We will include such a tabular listing in a revision of the labeling; Post-text Table 5.2.1 in Section 2.7.4, starting on page 64 of 180.

FDA Comment 2:

Please indicate where in the submission are the follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis. Please provide such data if not yet submitted.

Medicis response:

MP-0104-13 was closed after Hurricane Katrina destroyed the investigative site and the study subjects were scattered or lost. Additional follow-up is not available because the site has still not re-opened. Subjects with abnormal observations where follow-up is available was provided in Section 4.1 of the 120-day Safety Update submitted on November 16, 2005. In MP-0104-16 subjects were

observed at only one time point during long-term treatment and no non-treatment baseline assessment was done. Therefore, the return to baseline sperm analysis is not possible. Follow-up for several subjects with abnormal findings was provided in the response to FDA questions submitted as a minor amendment on November 16th 2005, as a part of the 120-day Safety Update within Section M5.3.5 of the eCTD.

FDA Comment 3:

Please submit photographs of subjects before and after treatment if available

Medicis response:

No photographs are available as the FDA approved protocols and informed consents did not provide for photography.

FDA Comment 4:

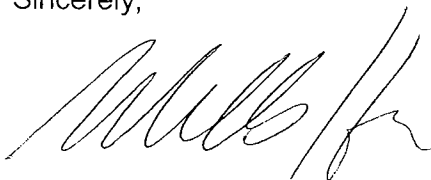
Have you submitted the protocols for the carcinogenicity studies to be conducted Phase 4 with minocycline? if so, where?

Medicis response:

Carcinogenicity studies to be conducted in Phase IV with minocycline were submitted on August 12th, 2006, and are included with this submission again for convenience as Attachment 1. We note that under ICH criteria and genotoxicity data, these studies are not required. Concerns raised in the academic community about a competitor product suggested that it would be beneficial to confirm that no such risk is suspected or exists with regards to Solodyn.

Should you have questions or need additional information, please do not hesitate to contact me or Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

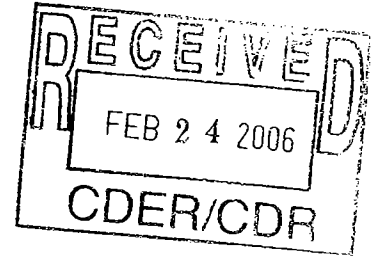
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FEB 28 2006



February 22, 2006

CDER White Oak DR1

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: ELECTRONIC DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

N 500-BZ

ELECTRONIC SUBMISSIONS

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release
45 mg, 90 mg and 135 mg**

ORIGINAL AMENDMENT

N(BZ)

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ (Minocycline Hydrochloride) Extended-Release
45 mg, 90 mg and 135 mg, submitted on June 30, 2005. Reference is also made to IND
65,398 submitted on July 12, 2002 in support of this NDA.

As requested by Felecia Curtis this morning, enclosed please find a disk compilation of the following submissions:

- December 22, 2005 Minor Amendment – Worldwide Safety Assessment
- January 16, 2006 Response to FDA Request (Pharmacokinetic)
- February 10, 2006 Labeling Amendment Response to FDA Request for FPL
- February 15, 2006 Response to FDA Request for Information (Pharm/Tox)
- February 16, 2006 Response to FDA Request for Information (Clinical)
- February 17, 2006 Response to FDA Request for Information (CMC)

All of the submissions were above were submitted as paper copies (archival and review) and accompanied by a disk that included an electronic copy of the submission except for the January 16, 2006, Pharmacokinetic Response.

The enclosed disk includes electronic copies of all of the above submissions in order for the Electronic Document Room to update the review files accordingly.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

Medicis Pharmaceutical Corporation
12901 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-808

INFORMATION REQUEST LETTER

Medicis Pharmaceutical Corp
Attention: Michele Wells
Vice President, Clinical Research and Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Mrs. Wells:

We are reviewing the Clinical and Pharmacology/Toxicology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. In the Solodyn label, please include the placebo group for comparison purposes in the tabulated list of adverse events for the < 5% group.
2. Please indicate where in the submission are the follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis. Please provide such data if not yet submitted.
3. Please submit photographs of subjects before and after treatment if available.
4. Have you submitted the protocols for the carcinogenicity studies to be conducted Phase 4 with minocycline? If so, where?

If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Sincerely,

{See appended electronic signature page}

Felecia Curtis

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
2/21/2006 01:50:54 PM
CSO



February 17, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Response to FDA Request for Information

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____ 45 mg, 90 mg and 135 mg, submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

In addition, reference is made to the February 15, 2006 FDA faxed filing communication, requesting information pertaining to the chemistry, manufacturing and controls section of the NDA.

Attached please find FDA's comments in ***bold italics*** followed by Medicis' responses to the February 15, 2006 FDA fax.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

dms



February 17, 2006

Caryn McNab
DHHS/FDA/ORAP-FO/LOS-DO
ATTN: Drug Preapproval Manager
Mail stop HFR-PA250
19701 Fairchild
Irvine, CA 92612-2506

Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____
45 mg, 90 mg and 135 mg

Dear Ms. McNab:

A field review copy of Medicis' February 17, 2006 Response to FDA's February 15, 2006 CMC Information Request for NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____ is enclosed.

I hereby certify that the enclosed documentation is a true copy of the archival and review copies of the response to FDA's February 15, 2006 CMC Information Request for NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Extended-Release _____ submitted to FDA headquarters in Rockville, MD.

This certification is provided in accordance with 21 CFR 314.50(l)(3).

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

dms

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
nt: Thursday, February 16, 2006 9:13 PM
Subject: Curtis, Felecia; Kozma-Fornaro, Mary J
Subject: NDA 50-808 Response to the Clinical Information request of 2/9

Attachments: 356h.pdf; cover.pdf; Attachment1.pdf; Attachment2 .pdf; emfalert.txt



356h.pdf (162 KB)



cover.pdf (166 KB)



Attachment1.pdf
(463 KB)



Attachment2 .pdf
(224 KB)



emfalert.txt (2 KB)

Felecia -

Here is an electronic copy of our response to the Clinical Information request.

You should have received the Monkey Study submission this morning.

This submission will be sent via Fed Ex tomorrow, so you will receive your desk copy on Tuesday, February 21 (after the Monday holiday).

We have now completed a labeling amendment on 2/10 (mock final labeling), On 2/15 we filed the response to the Pharm Tox Info (Monkey Study), and today 2/16 we're filing the Clinical Information requested.

I believe that that leaves the only open request as the 2/15 request for CMC information, due to FDA by 2/22.

It is helpful when you define a due date for us because I can put more pressure on the team to push the submission along faster. I really appreciate your help. I am sorry for the delays with the Monkey Study, but it is not complete and we had to push for an preliminary report. Thanks for conveying the sense of urgency.

Please don't hesitate to contact me with any requests for additional information. You may call directly on my cell at 480 221 9968.

Regards,
Michelle

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800

Direct: 602 808 3851

Fax: 602 778 6051

Cell: 480 221 9968

mwells@medicis.com <<mailto:mwells@medicis.com>>



February 16, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Response to FDA Request for
Information**

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™, Modified Release submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the February 9, 2006 FDA faxed filing communication, providing a request for Clinical Information submitted in the NDA filing for this product.

Below please find FDA's comments in *italics* followed by Medicis' responses to the February 9, 2006 FDA fax.

FDA Comment:

1. *Do you have further information for the worldwide safety update?*

We have not re-run the literature search since our submission of the worldwide safety update. However, we continuously monitor the literature for adverse event reports as part of our pharmacovigilance of our marketed minocycline products, and no new publications have come to our attention. We provide a literature update as part of our annual report for minocycline products, submitted in June of each year or sooner as required.

2. *Can the literature report update be broken out for the acne specific reports?*

The worldwide safety update submitted in December was divided into specific sections. Included with this letter as Attachment 1 are those portions of the worldwide safety assessment that deal with acne, specifically:

Section 2: Acne Review Articles
Section 2.1 Minocycline Safety Review
Section 3: General Acne Review Articles
Section 5.2 Acne Case Reports

3. Please provide the pregnancy outcomes for the following subjects (if already provided, please indicate location)

MP-0104-04 subjects 32/4, 32/22, 42/66, 49/30

Following are pregnancy outcomes for subjects 32-004, 32-022, 42-066 and 49-030. The table below encapsulates the information on the reports.

Subject #	Treatment	Outcome
32-004	Active	Subject miscarried
32-022	Active	Subject had an elective abortion
42-066	Placebo	Subject delivered prematurely
49-030	Placebo	Unknown

Subject 32/4, a 22-year old Black female, began treatment with 1 mg/kg minocycline on 21 July 2004. At the [redacted] visit on [redacted], the subject had a negative pregnancy test. The subject discontinued the study medication on [redacted] because she found that she was pregnant, and was seen for an early termination visit on [redacted] at which time the pregnancy was confirmed with a positive pregnancy test. Her last menstrual cycle was [redacted]. The subject had a spontaneous miscarriage or [redacted]. The site reports that, despite repeated telephone and written attempts, they are unable to contact the subject for follow-up information.

Subject 32/22, a 24-year old White female, began treatment with 1 mg/kg minocycline on 16 August 2004. The subject completed the study per protocol. On [redacted] at the Day [redacted] visit, a urine pregnancy test was found to be positive. The subject's last menstrual cycle was [redacted]. The urine pregnancy test completed at her [redacted] visit on [redacted] was negative. The subject returned for the Day 112 visit on 6 December 2004. The subject had an elective abortion on [redacted].

Subject 42/66, an 18-year old White female, began treatment with placebo on 19 August 2004. This pregnancy was reported as a non-serious adverse event (dates unknown) for which the subject was discontinued from the study on 11 November 2004 (Day 85). The last day of study medication was 14 October 2004 (Day 57). The subject did not return for the Day 56 study visit, but returned for the termination visit on 11 November 2004. The subject's last menstrual period was in [redacted]. The subject had a negative pregnancy test at her [redacted] visit on [redacted]. The subject delivered a pre-mature infant girl by emergency C-section on [redacted]. The infant had surgery for patent ductus arteriosus (PDA). On [redacted], the infant passed away. Cause of death was listed as Sudden Infant Death Syndrome (SIDS).

Subject 49/30, a 36-year-old Black female, began treatment with placebo on 9 July 2004. The MP-0104-04 report submitted in NDA 5-0808 reported in error on page 70 that the subject was receiving 1mg/kg minocycline. A subsequent review of the data confirms that the subject was on placebo treatment during the course of the study. A urine pregnancy test performed on [redacted] was negative. On [redacted] the urine pregnancy test was positive, and the study medication was discontinued that day. The pregnancy was confirmed by the subject's obstetrician/gynecologist on [redacted]. Her last menstrual period was [redacted]. The estimated date of delivery was [redacted]. The

pregnancy was reported by telephone, and the subject did not return for an early termination visit. The site reports that, despite repeated telephone and written attempts, they are unable to contact the subject for follow-up information.

MP-0104-05- Any pregnancies? (didn't note any)

There were no reported pregnancies in the MP-0104-05 study.

To provide the Division with a full update on the overall safety of the proposed product, Medicis is submitting an update to the information first provided in the 120-day Safety Update submitted December 21, 2006 regarding subjects with positive ANAs in the Phase III and Long-term safety studies. This information is included as Attachment 2.

To facility review, an electronic copy of the attachments is also included with this submission in a compact disk.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

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MEDICIS RECEIVED
FEB 17 2006

CDER White Oak DR1

RECEIVED
FEB 16

ORIG AMENDMENT

CDER CL

ORIGINAL

Response to FDA Request for Information

February 15, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

N 050-13P

Re: **NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™, Modified Release — submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the February 9, 2006 FDA faxed filing communication, providing a request for Pharmacology Toxicology information pertaining to study — 450012, 9-month monkey study, submitted in the NDA filing for this product.

Below please find FDA's comments in *italics* followed by Medicis' responses to the February 9, 2006 FDA fax.

FDA Comment:

Please provide an updated complete report of study No. — 450012, 9-month monkey study. An August 25, 2005 submission was a "Modified: 8/25/0": unaudited draft report of the 9-month monkey study. The full study should be completed at this time and we would appreciate a more complete updated report submission. Please advise when it will be available and submit ASAP if ready for submission at this time. If not ready for submission, please advise as to expected submission date.

Medicis Response

Attached is an updated unaudited summary report (Attachment 1) of the 9-month monkey study. The dosing phase of the study was completed and necropsy done on December 1-2, 2005. After discussions with the lab and our toxicology consultant, and based on a review of the literature, Amendment 1 to the protocol (Attachment 2), extending the recovery period from 1 month to 3 months was initiated on December 22, 2005. Two animals of each sex from the control and high dose groups are included in the recovery group. We believe extending the recovery period was a prudent step as this was the first long-term study of minocycline in primates and should provide us with information that more fully demonstrates the residual effects of long-term dosing on these animals.

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

FDA Fax Memo

Date: February 15, 2006

Subject: **NDA 50-808 CMC IR**

Hi Michele;

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please note the revised #10.

- (10). The average and range of tablet hardness for all 3 strengths are similar. No specification is proposed. Include tablet hardness as an in-process test "for information only".
 - (11). It is stated for several dissolution data points that "Dissolution mean is more than 5.0% absolute difference higher than the assay results". Please explain this difference.
 - (12). The development efforts were initiated for an extended release formulation with 2 prototypes dissolving, i.e., 90% dissolution, one prototype dissolved after 4 hours and the second one after 6 hours. Provide a rationale for the selection of these prototypes.
 - (13). It is stated to refer to drug substance DMF for stability data. How is the expiration date established?
 - (14). The proposed specification for the drug product is not more than — The moisture data ranges from a low of — to a high of —. Stability data for all registration lots in each packaging configuration remained within specifications, however, the proposed acceptance criteria is considerably wider than the moisture data for the proposed formulation. No data for tablet hardness and dissolution was provided in the Pharmaceutical Development section at high moisture content (——). Please calculate the theoretical moisture content for the various caplet strengths and based on the theoretical moisture content and actual stability data, revise moisture specification.
 - (15). Please provide a specific storage time for the resolution solution in the HPLC assay with an added statement to discard the solution if there is significant interference in the peak separation when the solution is stored under specified storage condition and time.
-

(17).

Since tablet strength is for minocycline, include minocycline hydrochloride in the package insert. Thus the establish name of the drug product is (Minocycline Extended -release Tablet). Please explain if there is any concern for this recommendation.

Please submit this information by COB on February 22, 2006. If you have any questions, call Felecia Curtis, Regulatory Project Manager, at 301-796-0877.

Respectfully,
Felecia Curtis

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/s/

Felicia Curtis
2/15/2006 01:58:02 PM
CSO

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Content: Friday, February 10, 2006 4:37 PM
Subject: Curtis, Felecia; Kozma-Fornaro, Mary J
NDA 50-808



021006 NDA

50-808 Labeling Ame.



emfalert.txt (1 KB)

Attached is a copy of the labeling amendment you requested on February

2. We have completed the label design, and the submission consists of color paper copies and electronic copies of the proposed labeling in FPL format, using the currently proposed tradename: Solodyn.

Since the files are large, I have attached only the cover letter to this e-mail. However, a desk copy is being sent directly to Felecia and includes a CD with all the submitted labeling.

Please let me know if you have questions or need additional information. As always, thanks so much for your help.

Regards,
Michelle

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800
Direct: 602 808 3851
Fax: 602 778 6051
Cell: 480 221 9968

mwells@medicis.com <<mailto:mwells@medicis.com>>



The Dermatology Company®

February 10, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Labeling Amendment
Response to FDA Request for FPL

Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release
45 mg, 90 mg and 135 mg

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™, Modified Release submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

In addition, reference is made to the February 2, 2006 telephone contact between Felecia Curtis, Regulatory Project Manager at FDA and _____ Associate Director Regulatory Affairs, during which a request for Final Printed Labeling was made.

Pursuant to 21 CFR 314.60, Medicis hereby submits this Response to the February 2, 2006 FDA Labeling Request with regard to the pending New Drug Application (NDA) 50-808 for SOLODYN™ (Minocycline Hydrochloride) Modified Release _____

The enclosed labeling has been revised only in format and layout. No text changes have been made from the original NDA submission on June 30, 2005. The Word package insert is enclosed to facilitate review. The package insert remains unchanged from the amendment filed on November 16, 2005.

The composition of the materials utilized in the fabrication of the _____ remains the same. Medicis commits to filing details regarding this change in the first CMC amendment filed to this application.

To facilitate review, this submission contains tables of contents reflecting the organization of our response as submitted on compact disk and in hard copy.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

NDA 50-808

Clinical Information Request

1. Do you have further information for the worldwide safety update?
2. Can the literature report update be broken out for acne specific reports?
3. Please provide the pregnancy outcomes for the following subjects (If already provided, please indicate location)

MP-0104-04 - Subjects 32/4, 32/22, 42/66, 49/30.

MP-0104-05 - Any pregnancies ? (Didn't note any)

Thank you.

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/s/

Mary Jean Kozma Fornaro
2/9/2006 12:47:34 PM
CSO

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

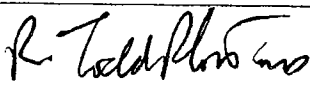
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME R. Todd Plott, M.D.	TITLE V.P. Clinical Research and Regulatory Affairs
FIRM / ORGANIZATION Medicis Pharmaceuticals	
SIGNATURE 	DATE 6/7/05

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

NDA 50-808

Pharmacology Toxicology Information Request:

Please provide an updated complete report of study No. ~~4~~-450012, 9-month monkey study.

An August 25, 2005 submission was a “ Modified: 8/25/05” unaudited draft report of the 9-month monkey study.

The full study should be completed at this time and we would appreciate a more complete updated report submission. Please advise when it will be available and submit ASAP if ready for submission at this time.

If not ready for submission, please advise as to expected submission date.

Thank you.

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/s/

Mary Jean Kozma Fornaro
2/8/2006 02:59:44 PM
CSO

NDA 50-808

Chemistry Information Request:

1). It is stated that excipient compatibility studies were conducted to support the use of the selected excipients but no data was provided. Please provide this information.

(3). Please provide the rationale for selection of the dissolution method for the prototype tablet dissolution testing.

(5). Please confirm if there is any plan for reprocessing a failed batch?

(6). Please provide justification for the proposed dissolution specifications based on the biopharmaceutical considerations (data on formulations that failed dissolution as well as bioavailability).

(7). Confirm if all three tablets strengths were used in Phase III clinical studies.

(8). Confirm if any of the tablet has a bisect line.

(9). Two lots (Lot # 03292C, 135 mg caplet, _____, Phase III study p.136 and Lot #03291C, 90 mg caplet, _____, Phase III study, p. 101) required Stage 2 and Stage 3 under USP dissolution test for the _____ stored under 25°C/60% RH for 1 and 3 months. Additional data reported on page 135 for the 135 mg _____ and page 100 for the 90 mg caplet did not require Stage 2, Stage 3 data to meet the acceptance criteria. The tablet crushing data(hardness) does not support the slower dissolution (data reported on pages 129 and 101 for the 135 and 90 mg _____ respectively). Also, the moisture data is well within the range _____). Please explain why some samples failed Stage 1 dissolution.

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10). The average and range of tablet hardness for all 3 strengths are similar. No specification is proposed. However, please propose in-process acceptance criteria.



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this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
1/31/2006 03:32:27 PM
CSO



January 16, 2006

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**Response to FDA Request for
Information**

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release [REDACTED]
45 mg, 90 mg and 135 mg**

Dear Dr. Kukich:

Reference is made to NDA 50-808, SOLODYN™, Modified Release [REDACTED], submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the January 9, 2006 FDA faxed filing communication, providing a request for pharmacokinetics information pertaining to study MP-0104-15 submitted in the NDA filing for this product.

Below please find FDA's comments in *italics* followed by Medicis' responses to the January 9, 2006 FDA fax.

FDA Comment #1:

Explain why there was a persistent period/sequence effect on the PK parameters observed in the study.

Medicis Response

We have considered several possible reasons for the differences observed between the subjects treated with reference drug followed by test drug (Group 1) and test drug followed by reference drug (Group 2). Three possibilities which may explain this observation and are clearly presented in the redrawn figures presented in Attachment 1 (in response to FDA's comment #3 below) and discussed in detail below. As discussed in the report, there was a statistically significant difference between the two groups observed across steady state PK parameters for Days 5 to 7. However, in a 2-way crossover design, the sequence effects may be confounded by drug carryover and treatment-by-period interactions.

In this study, the shapes of the steady-state mean plasma concentration vs. time curves were similar between sequence groups for each treatment. Thus, the curve for the reference treatment in Period 1 is similar in shape to the curve for the reference treatment in Period 2, and the same is true of the test treatment curves. Only the magnitudes of the mean AUC are greater for Sequence Group 1 compared to Sequence Group 2. The mean AUC for Reference in Period 1 was 54.1 ng-hr/mL; mean AUC for Reference in Period 2 was 38.6 ng-hr/mL; mean AUC for Test in Period 1 was 28.4

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

ng-hr/mL; and for Test in Period 2, it was 38.3 ng-hr/mL. Therefore, the 3 most reasonable interpretations of the observed effect in this study:

- (1) If the effect were interpreted as a drug carryover effect due to treatments, one would have to postulate that the Reference treatment had a large negative carryover effect and the Test treatment had a smaller positive carryover effect. This conclusion would be illogical, as one would expect a carryover effect to increase the AUC, not reduce the AUC.
- (2) If the effect is interpreted as a period-by-treatment interaction, one would have to postulate that the pharmacokinetics of the two treatments were quite different in the first period, but very similar in the second period. This conclusion would also be illogical.
- (3) If the effect is interpreted as a sequence effect, then one would have to conclude that by chance the subjects randomized to Sequence Group 1 had greater steady state minocycline levels than the subjects randomized to Sequence Group 2, after adjustment for the significant treatment differences.

Of these three interpretations, the third would appear to be most likely. It would be difficult to suggest properties of the two formulations that would result in such large differential carryover effects, or period-dependent conditions, which would result in large differences in the relative treatment effects. It is noteworthy that the ratio of mean AUC (Test/Reference) for Sequence Group 1 is approximately equal to the ratio of mean AUC (Test/Reference) for Sequence Group 2 (0.707 and 0.735, respectively). This is consistent with an explanation of the sequence effect based on within subject variability, independent of treatment formulation and confounded by the study design which was outpatient until Day 6 when subjects were confined in the clinic until the morning of Day 7.

FDA Comment #2:

As the data reveals that trough level of minocycline was still increasing following Day 7, explain how the study can be qualified as a steady state study.

Medicis Response:

The design of the steady state pharmacokinetic study allowed for observations of blood levels after 5 half-lives ($T_{1/2}$ = 14 to 18 hours for minocycline); typically a point where steady state conditions are expected to be observed. After 5 half lives and during Days 4, 5 and 6 trough blood levels of the test product were stable. Statistically, the test drug levels on these days were not significantly different. Medicis believes that the data obtained in this study represents a steady state. Also the study design was an outpatient study until Day 6 which allowed patients to take their medication with or without food on all study days, EXCEPT on Day 6 when the study medication was administered in a fasting state during inpatient confinement. Twenty-four hours later, Day 7 trough levels were obtained. Therefore it would not be unexpected that steady state trough levels obtained on Day 4, 5, and 6 (fed state) might be slightly lower than on Day 7 (fasting conditions) because the AUC under fasting conditions is slightly greater than in the fed state.

Further, the dose-adjusted trough levels of the test product were below the reference drug level suggesting that the lower overall drug exposure to minocycline delivered by the new formulation than is currently used. Clinical studies during Phase 3 have shown that the modified release Minocycline HCl are safe and effective in patients with moderate-to-severe acne vulgaris when treated over at least a 12 week period of time. The reference drug has been used chronically for >20 years in the treatment of acne and the test product has long-term safety data provided in the NDA.

FDA Comment #3:

Redraw the Figures (Mean Dose-Adjusted Plasma Minocycline Trough Concentrations By Period, By Treatment for All Completed Subjects (N=27) and Mean Dose-Adjusted Day 6 Plasma Minocycline Concentrations By Period, By Treatment for All Completed Subjects (N=27) with SD/SE bars for each point.

Medicis Response

Attachment 1 presents figures for Mean Dose-Adjusted Plasma Minocycline Trough Concentrations by Period by Treatment for All Completed Subjects (N=27) and Mean Dose-Adjusted Day 6 Plasma Minocycline Concentrations by Period by Treatment for All Completed Subjects (N=27) with bars at each time point showing 1 standard error of the mean (SE). (Fasting levels on Day 7)

Medicis is eager to assist the Agency in answering any other questions that may arise in this application. Never the less, we believe the objectives of this study to evaluate the pharmacokinetics of this formulation have been met and confirm the bioavailability and slower rate of absorption of the product. Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

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Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Monday, January 16, 2006 4:16 PM
To: Kozma-Fornaro, Mary J; Curtis, Felecia
Subject: RE: Fax regarding NDA 50-808

Attached is a copy of our complete response which you should receive when you return to the office tomorrow.

Felicia - a desk copy should be delivered directly to you.

Please don't hesitate to contact me with questions.

Regards,
Michelle

-----Original Message-----

From: Kozma-Fornaro, Mary J [mailto:KOZMAFORNARO@cder.fda.gov]
Sent: Friday, January 13, 2006 10:43 AM
To: Michelle Wells; Curtis, Felecia
Subject: RE: Fax regarding NDA 50-808

Michelle,

Received the requested information. Felecia is out today so thank you for copying me. I forwarded to the reviewer.

I checked the fax machine and paper is in the system so I am not sure what the problem is. This email receipt is sufficient.

Our other fax number (for the future if needed) is 301 796-9895.

Thanks Mary Jean

-----Original Message-----

From: Michelle Wells [mailto:mwells@medicis.com]
Sent: Friday, January 13, 2006 12:13 PM
To: Curtis, Felecia
Cc: Kozma-Fornaro, Mary J
Subject: Fax regarding NDA 50-808

Attached please find a copy of a fax I have been trying to send to both 301 796 9894 but the fax is not going through. Also, I have not received a call back for guidance as to how to best provide this information to you.

Per my voicemail message I left this morning, I am providing the available information we have to respond to your fax dated January 9, 2006, in which a response is requested by noon today.

Attached please find the revised figures as requested. We are completing our review of the narrative response and will be able to provide that formally by fax by the end of the day, with an official hard copy following by Fed Ex next week. I will have a desk copy provided to you as well.

Should you have questions or need additional information, please do not hesitate to contact me direct at 602 808 3851 or on my cell phone at 480 221 9968. Feel free to call me on my cell phone anytime, even at Eastern Time.

<<Fax MW-FC 011306.doc>> <<Pages 4- 7 from cover 011306 PK Response Adobe.pdf>>

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800
Direct: 602 808 3851
Fax: 602 778 6051
Cell: 480 221 9968

mwells@medicis.com <<mailto:mwells@medicis.com>>

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Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Friday, January 13, 2006 12:13 PM
To: Curtis, Felecia
Cc: Kozma-Fornaro, Mary J
Subject: Fax regarding NDA 50-808

Attached please find a copy of a fax I have been trying to send to both 301 796 9894 but the fax is not going through. Also, I have not received a call back for guidance as to how to best provide this information to you.

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<<Fax MW-FC 011306.doc>> <<Pages 4- 7 from cover 011306 PK Response Adobe.pdf>>

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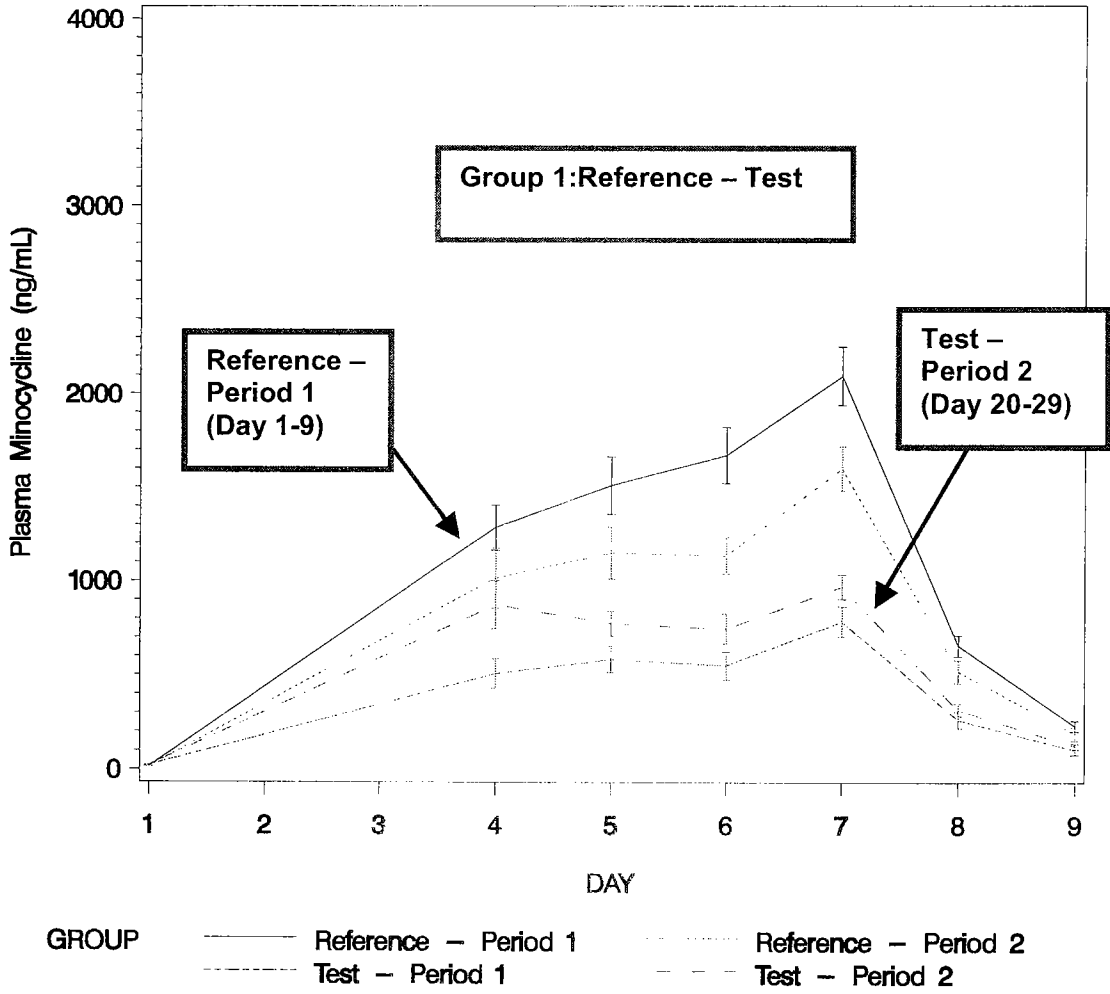
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NDA 50-808
RESPONSE TO PK INFORMATION REQUEST OF 9 JANUARY 2006
ATTACHMENT 1

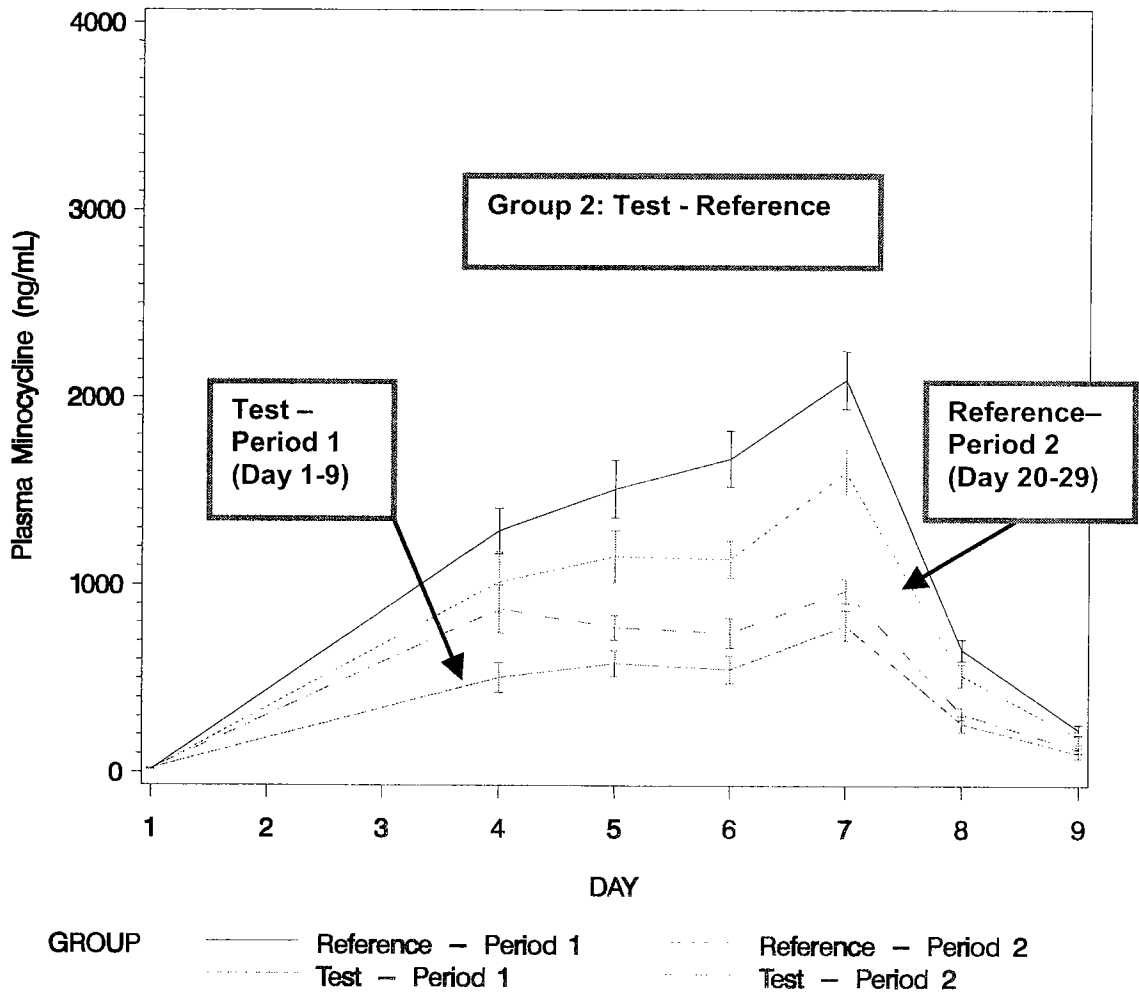
Mean Dose-Adjusted Plasma Minocycline Trough Concentrations by Period by Treatment for All Completed Subjects (N=27)

Error bars show 1 standard error of the mean (SE).

Plasma Minocycline Levels, Dose-Adjusted
Days 1 through 9 - Average Over All Subjects



Plasma Minocycline Levels, Dose-Adjusted
Days 1 through 9 - Average Over All Subjects

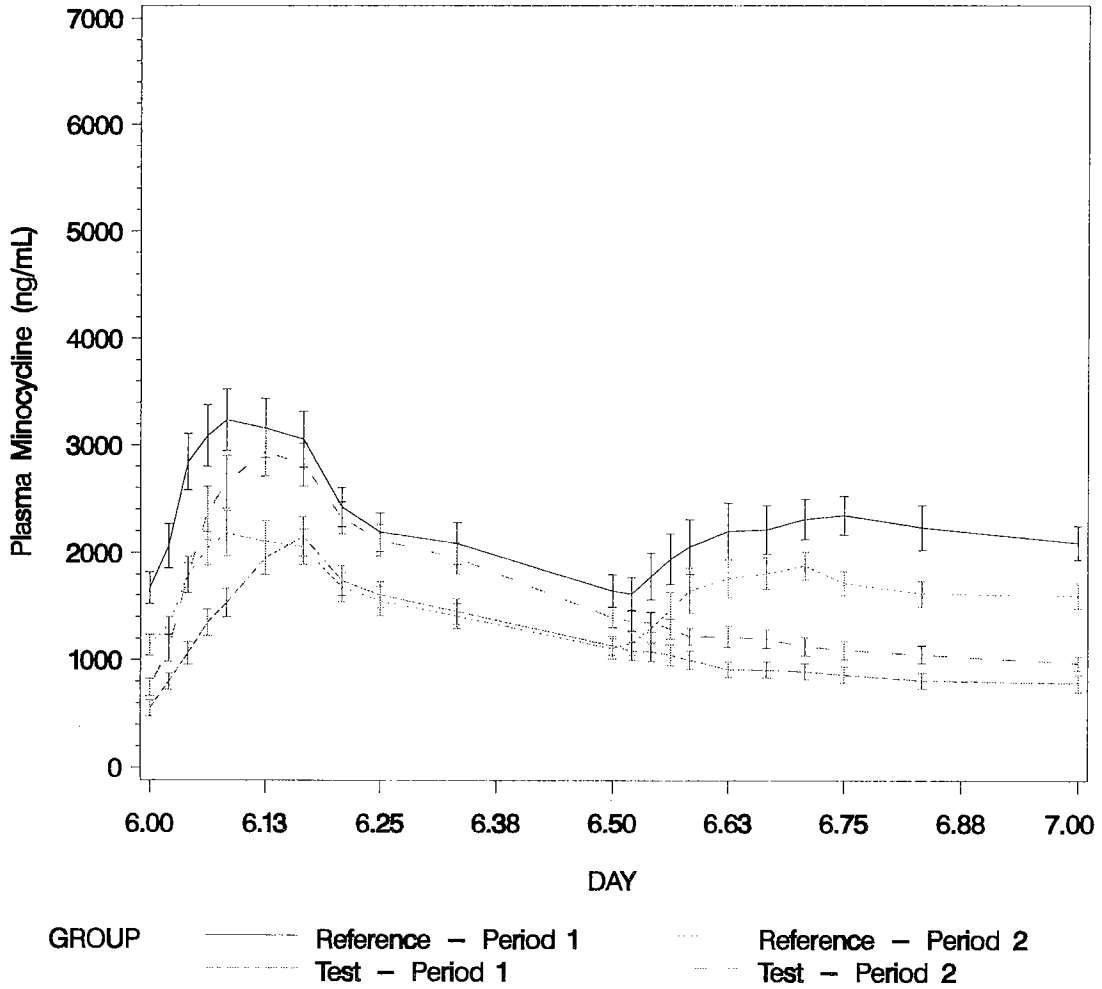


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Mean Dose-Adjusted Day 6 Plasma Minocycline Concentrations by Period by Treatment for All Completed Subjects (N=27)

Error bars show 1 standard error of the mean (SE).

**Plasma Minocycline Levels, Dose-Adjusted
Day 6 - Average Over All Subjects**



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FDA Fax Memo

January 9, 2006

NDA 50-808

Dear Ms. Wells,

Pharmacokinetics information request

Please refer to your July 8, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Solodyn (minocycline hydrochloride).

We are reviewing the Pharmacokinetics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

All the following bullets are for Study MP-0104-15.

- Explain why there was a persistent period/sequence effect on the PK parameters observed in the study
- As the data reveals that trough level of minocycline was still increasing following Day 7, explain how the study can be qualified as a steady state study.
- Redraw the Figures (*Mean Dose-Adjusted Plasma Minocycline Trough Concentrations By Period, By Treatment for All Completed Subjects (N=27)* and *Mean Dose-Adjusted Day 6 Plasma Minocycline Concentrations By Period, By Treatment for All Completed Subjects (N=27)*) with SD/SE bars for each point.

Please respond by noon on January 13, 2006. If you have questions, please contact me at (301) 796-0877.

Respectfully,
Felecia Curtis

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On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
1/9/2006 11:34:40 AM
CSO

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: August 23, 2005	DESIRED COMPLETION DATE: January 15, 2006	ODS CONSULT #: 05-0214
DATE OF DOCUMENT: June 30, 2005	PDUFA DATE: May 8, 2006	

TO: Stanka Kukich, M.D.
Acting Director, Division of Dermatology and Dental Products
HFD-540

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Solodyn™ (Minocycline Hydrochloride) Modified Release 45 mg, 90 mg, and 135 mg NDA #: 50-808	SPONSOR: Medicis
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RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Solodyn. This is considered a tentative decision, and the firm should be notified that this name, with its associated labels and labeling, must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review to minimize potential errors with the use of this product.
3. DMETS consulted the CDER Labeling and Nomenclature Committee (LNC) concerning the established name. The LNC recommends the dosage form be designated as "tablet" with reference to the _____ in the package insert. The LNC also recommends "modified release" be revised to either "extended" or "delayed release." For input on which designation is most appropriate, contact Guiragos Poochikian of the LNC.
4. DDMAC finds the proprietary name Solodyn acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-5038.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Solodyn." Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and professional experiences in addition to a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Solodyn.
2. The Expert Panel and independent review identified seventeen proprietary names that were thought to have potential for confusion with Solodyn. These products are listed in Table 1 (see below, page 4 and 5), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other*
Solodyn (Rx)	Minocycline Modified-Release ██████████ 45 mg, 90 mg, and 135 mg	Once daily dosing based on weight (1mg/kg). Average 45 to 135 mg daily.	
Salagen (Rx)	Pilocarpine Hydrochloride Tablets, 5 mg and 7.5 mg	<u>Head and Neck Cancer</u> : Initially, 5 mg three times daily- up to 15 to 30 mg per day. <u>Sjogren's Syndrome</u> : 5 mg four times daily. <u>Hepatic impairment</u> : 5 mg twice daily.	LA
Solatene	Beta-carotene Capsules 30 mg	30 mg to 300 mg per day.	SA
Solaquin (OTC) Solaquin Forte (Rx)	Hydroquinone 2% Cream Hydroquinone 4% Cream and Gel (28.35 gm)	Apply twice daily.	SA
Talacen (Rx)	Acetaminophen and Pentazocine Hydrochloride Tablets, 650 mg/25 mg	One tablet every 4 hours, up to six tablets per day.	LA
Lodosyn	Carbidopa Tablets, 25 mg	Do not exceed 200 mg. 25 mg may be given with the first dose of carbidopa/levodopa with additional doses of 12.5 to 25 mg with each dose.	LA
Silvadene	Silver Sulfadiazine Cream (10 mg per gram in a water-miscible base) 20, 50, 85, 400 and 1000 grams	Apply once or twice daily to a thickness of approximately $\frac{1}{16}$ inch to the clean and debrided wound.	SA
Sarafem Pulvules	Fluoxetine Capsules 10 mg, 20 mg	Initial: 20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle). Do not exceed 80 mg/day.	LA/SA
Ser-a-gen	Hydralazine Hydrochloride, Hydrochlorothiazide and Reserpine, 25 mg/15 mg/0.1 mg	One to two tablets three times daily.	SA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other*
Solodyn (Rx)	Minocycline Modified-Release 45 mg, 90 mg, and 135 mg	Once daily dosing based on weight (1mg/kg). Average 45 to 135 mg daily.	
Serostim Serostim LQ	Somatropin Powder for Injection 4 mg (12 units), 5 mg (15 units), 6 mg (18 units) (Single-use vials with diluent), 8.8 mg (26.4 units) auto-injector 6 mg per 0.5 mL	0.1 mg/kg subcutaneously daily, up to 6 mg.	SA
Normodyne	Labetolol Tablets (generic only) 100 mg, 200 mg, 300 mg Injection: 5 mg/mL (20 mL and 40 mL multidose vials)	Initial dose: Individualize dosage. 100 mg twice daily, Maintenance dose: 200 to 400 mg twice daily. Repeated IV injection: Initially, 20 mg (0.25 mg/kg for an 80 kg patient) slowly over 2 minutes. Additional injections of 40 or 80 mg can be given at ten minute intervals until a desired supine BP is achieved or a total of 300 mg has been injected. Slow continuous infusion: Dilute. Either add 200 mg to 160 mL of IV fluid to prepare 1 mg/mL solution at a rate of 2 mL/min (2 mg/min). Or, 200 mg to 250 mL of an IV fluid to prepare 2 mg/3 mL solution; give at a rate of 3 mL/min (2 mg/min).	SA
Duradyne DHC	Hydrocodone Bitartrate and Acetaminophen Tablets, 5mg/500 mg	1-2 every 4 to 6 hours.	LA/SA
Sonazine	Chlorpromazine Hydrochloride Syrup: 30 mg/mL, 100 mg/mL, 10 mg/5mg	<u>Psychotic Disorders:</u> 10 mg to 25 mg 3 to 4 times per day. <u>Behavioral Disorders:</u> 0.5 mg/kg (0.25 mg/lb) every 4 to 6 hours, as needed. If hospitalized, 50 to 100 mg/day, or in older children, 200 mg/day or more may be necessary. <u>Preoperative apprehension:</u> 25 to 50 mg orally 2 to 3 hours before surgery. <u>Preoperative apprehension (children):</u> 0.5 mg/kg (0.25 mg/lb) orally 2 to 3 hours before operation. <u>Acute intermittent porphyria (adults):</u> 25 to 50 mg orally 3 or 4 times/day <u>Nausea and vomiting: Adults</u> Oral: 10 to 25 mg every 4 to 6 hours, as needed; increase if necessary. <u>Children:</u> 0.25 mg/lb (0.55 mg/kg) every 4 to 6 hours, as needed. <u>Intractable hiccoughs:</u> Orally, 25 to 50 mg 3 or 4 times daily.	LA/SA
Stavudine Zerit XR	D4T (Zerit) Capsules 15 mg, 20 mg, 30 mg and 40 mg Powder for Oral Solution: 1 mg/mL when reconstituted Capsules 37.5 mg, 50 mg, 75 mg, 100 mg	40 mg every 12 hours (>60 kg) 30 mg every 12 hours (< 60kg) <u>Children:</u> 0.5 mg/kg/dose every 12 hours (birth to 13 days), 1 mg/kg/dose every 12 hours for at least 14 days of age <u>Extended release:</u> 100 mg daily (> 60 kg) 75 mg daily (< 60kg)	SA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other*
Solodyn (Rx)	Minoxidil Modified-Release 45 mg, 90 mg, and 135 mg	Once daily dosing based on weight (1mg/kg). Average 45 to 135 mg daily.	
Stelazine	Trifluoperazine Hydrochloride Tablets 1 mg, 2 mg, 5 mg and 10 mg	Schizophrenia: Adults: 2 to 5 mg orally twice daily. optimum responses seen with 15 or 20 mg/day, up to 40 mg/day or more. Children (6 to 12 years of age): Initial dose is 1 mg once or twice daily. Usually not necessary to exceed 15 mg/day. Nonpsychotic anxiety: 1 or 2 mg twice daily.	SA
Razadyne	Galantamine Hydrobromide Tablets: 4 mg, 8 mg, 12 mg Oral Solution: 4 mg/mL	16 to 32 mg/day given twice daily with a starting dose of 4 mg twice daily.	LA
Razadyne ER	Capsules: 8 mg, 16 mg and 24 mg	16 to 24 mg/day with a starting dose of 8 mg per day.	
Visudyne	Verteporfin Lyophilized Cake for Injection 15 mg, reconstituted to 2 mg/mL	A course of therapy is a 2-step process requiring administration of both drug and light. 6 mg/m ² body surface area (BSA)	LA
Zolpidem	Zolpidem Tartrate (Ambien) Tablets, 5 mg and 10 mg	10 mg before bedtime.	SA
Zolpidem (CR)	Tablets, 6.25 mg and 12.5 mg	12.5 mg before bedtime.	

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Solodyn were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Solodyn with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 121 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Solodyn (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Solodyn 45mg #30 Take 1 tablet daily</p>	<p>Solodyn 45 mg #30 Take one tablet daily</p>
<p><u>Inpatient RX:</u></p> <p>Solodyn 45mg T QD</p>	

2. Results:

In the verbal study, three participants identified the proposed name as Silvidin, Silavden and Sulvaden that are phonetically similar to the currently marketed drug product of Silvadene. Another participant identified the proposed name as Zoliden that is phonetically similar to the currently marketed drug product of Zolpidem. A third name, Solidex, was identified in the verbal study that is similar to "Solidax", an over-the-counter weight loss medication. In the outpatient study, eighteen identified the name as "Solodyne", which is a bisodyne detergent sanitizer. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Solodyn", the products considered to have potential for name confusion with Solodyn include: Salagen, Solatene, Solaquin, Talacen, Lodosyn, Silvadene, Sarafem, Ser-a-gen, Serostim, Normodyne, Duradyne, Sonazine, Stavudine, Stelazine, Razadyne, Visudyne, and Zolpidem.

Upon review of the names gathered from EPD and independent review, Sarafem, Ser-a-gen, Serostim, Normodyne, Duradyne, Sonazine, Stavudine, Stelazine, and Visudyne will not be analyzed further. In addition to a lack of convincing look-alike and sound-alike potential, these products were not reviewed for the following reasons: Ser-a-gen was withdrawn from the marketplace in 1994 and no generics are available. Duradyne was withdrawn in 1993. Although there are generic drug products marketed, Duradyne does not overlap in strength or dosing with Solodyn. Although data is available in some medical sources and on the web for Sonazine, the drug product does not appear to be available for purchase in the US marketplace and lacks overlapping strength and dosing frequency. Sarafem, Normodyne, Stavudine, and Stelazine differ in strength. Serostim and Visudyne differ in strength and route of administration.

DMETS would also like to acknowledge that a search found multiple look-alike and sound-alike medications marketed in other countries, which are as follows: Solidon (chlorpromazine in Greece), Zoliden (ranitidine in Greece), Salodan/Seladin (naproxen in Japan, Malaysia and Taiwan), Sulidin (nimesulide in Turkey), Sulidene (nimesulide in France), Zolidin (dipyron in Mexico), Solufen (ibuprofen in South Africa, France and Spain and containing chloramphenicol in Mexico), Soludin (antiseptic/disinfectant in Ecuador, last sales were seen in 2003), Sulidan (non-steroidal/antirheumatic in Egypt), Zuledin (antipsychotic in Greece), Zeladin (antacid in Korea), Seladon (non-narcotic analgesics/antipyretic in Korea), Salidon (cold preparation in Pakistan with last recorded sales in 1997), and Zolidin (non-steroidal/antirheumatic in Thailand). For these drug products, the available information on the web and in reference texts are limited. Thus, although the look-alike and sound-alike characteristics are apparent, DMETS believes the actual possibility for confusion with these product names to be minimal due to the areas of marketing.

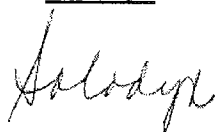
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, there were two names, Silvadene and Zolpidem, identified due to their phonetic similarity to participant interpretations of Solodyne. In the verbal study, three participants identified the proposed name as Silvidin, Silavden and Sulvaden that are phonetically similar to the currently marketed drug product of Silvadene and another participant identified the proposed name as Zoliden that is phonetically similar to the currently marketed drug product of Zolpidem. In addition, one additional verbal participant identified "Solidax", which is similar to Solidex, an over-the-counter, web purchased only weight loss medication. In the outpatient study, eighteen identified the name as "Solodyne", which is a bisodyne detergent sanitizer. The names Solidex and Solodyne will not be reviewed further as DMETS can not rationalize a situation where medication error could occur. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Solodyne. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

The remaining names of Salagen, Solatene, Soloquin, Talacen, Lodosyn, Silvadene, Razadyne and Zolpidem will be reviewed in detail below.

1. Salagen was identified to look similar to the proposed name, Solodyn. Salagen contains pilocarpine hydrochloride in a tablet form for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck and treatment of dry mouth in patients with Sjogren's syndrome. The recommended initial dose for cancer patients is 5 mg three times daily, titrated to the usual dosage range of 15 to 30 mg per day. In Sjogren's syndrome, the patients take 5 mg four times daily. For either condition, the dose for patients with hepatic impairment is 5 mg twice daily.

The look-alike similarities between the names can be attributed to the presence of the beginning letter combinations "Solo" in Solodyn compared to "Sala" in Salagen, which can look similar. In addition, both names also end in the letter "n" with the downstroke of "y" in Solodyn and "g" in Salagen of similar placement. However, Solodyn contains the letter "d" with the distinct upstroke in the fifth position, which may help to distinguish the names. Solodyn and Salagen share an overlapping route of administration (oral) and dosage form (tablet). However, they differ in strength (45 mg, 90 mg, and 135 mg compared to 5 mg and 7.5 mg) and dosing frequency (three to four times per day compared to once daily). Although the products share some look-alike similarities, the potential for confusion between Solodyn and Salagen is minimized due to product differences.

Solodyn



Salagen



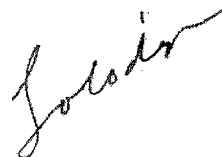
2. Solatene may sound similar to Solodyn when spoken, however this product was discontinued in 1996 and is not available in an equivalent generic formulation. This name is not readily available in commonly used references, such as Drug Facts and Comparisons, Physician's Desk Reference, the Orange Book, and the Red Book. However, this name is readily accessible on the web and drug@FDA. This marketing withdrawal reduced the therapeutic options for the treatment of erythropoietic porphyria. Thus, there are multiple medically significant web pages addressing alternatives (e.g. Brigham and Women's Hospital). DMETS can not envision a scenario where the prescription product Solodyn could be confused with Solatene, which is no longer marketed. Therefore, DMETS has minimal concerns with the

potential for confusion with Solodyn and Solatene.

3. Talacen was identified as looking similar to the proposed name, Solodyn. Talacen contains acetaminophen 650 mg and pentazocine 25 mg in a combination tablet for the treatment of mild to moderate pain. The recommended dosing is one tablet every four hours to a maximum of six tablets per day. The orthographic similarities stem from the "ala" of Talacen and "olo" of Solodyn, which may appear similar when scripted with the shared concluding "n." In addition, there is a limited possibility for the leading "T" of Talacen to resemble the "S" of Solodyn (see below). However, the upstroke of the "d" and downstroke of the "y" in Solodyn should help to differentiate the two names upon scripting.

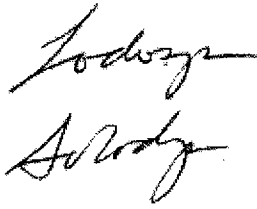
Talacen

Solodyn



Both Talacen and Solodyn are available in a tablet dosage form to be taken orally. However, there are distinguishable factors between Talacen and Solodyn that will decrease the potential for medication errors. Solodyn will be available in three dosage strengths (45 mg, 90 mg, or 135 mg), which do not overlap with the single strength of Talacen (650 mg/25 mg). Thus this will serve as a differentiating characteristic since strength must be present on the prescription order. In addition, the dosing frequencies do not overlap with Talacen, which is dosed every four hours compared to the daily dosing of Solodyn. Despite the orthographic similarities, the differences in product characteristics help to differentiate the two drug names.

4. Solaquin was identified to have verbal similarities to Solodyn. Solaquin contains hydroquinone 2% cream and 4% (Solaquin Forte) cream/gel for the gradual bleaching of hyperpigmented skin conditions. Both Solaquin and Solaquin Forte are to be applied twice daily. The phonetic similarities stem from the shared three syllable count, similar sounding leading letters ("Solo" vs. "Sola"), and similar sounding concluding letters (in, "-yn" vs. "-in"). However, the "q" of Solaquin and "d" of Solodyn should help to phonetically differentiate the names when spoken. Furthermore, Solaquin and Solodyn do not share any overlapping product characteristics, such as dosage form (cream compared to tablets), route of administration (topical compared to oral), dosing frequency (twice daily compared to once daily) and product strength (2% and 4% compared to 45 mg, 90 mg, and 135 mg). In addition, the Solaquin products are available in 30 gram tubes (28.35 gram); this numerical value does not overlap with the product strengths of Solodyn. Due to the differing products characteristics, DMETS believes the possibility for confusion to be minimal.
5. Lodosyn may look similar to Solodyn when scripted. Lodosyn contains carbidopa in a tablet formulation as an adjunct to therapy with levodopa for the treatment of Parkinson's disease. The dose is dependent on the needs of the patient, but is not to exceed 200 mg. The orthographic similarities stem from the possibility for the leading "L" and "S" to appear similar when scripted, which is followed by the similar "odo" of Lodosyn and "olo" of Solodyn and the shared upstroke ("d" and "l", respectively). This is further compounded by the shared concluding "yn." However, the upstroke of the "d" in Solodyn may differentiate the two names if prominent.



The two drug products share the oral route of administration and tablet form. However, they differ in frequency of dosing (likely three to four times daily compared to daily dosing) and strength (25 mg compared to 45 mg, 90 mg and 135 mg). Thus, DMETS believes the likelihood for confusion to be minimal due to differences in product characteristics as well a minimal look-alike potential.

6. Silvadene may sound similar to Solodyn when spoken. Silvadene contains silver sulfadiazine in a cream form for the treatment of burns. A 1/16 inch of medication is to be applied once or twice daily to a clean and debrided wound. In the verbal study, three participants identified the proposed name as Silvidin, Silavden and Sulvaden that are phonetically similar to Silvadene. The phonetic similarities stem from the shared three syllable count, shared leading "S", and similar concluding syllable of "dēn" of Silvadene and "dīn" of Solodyn. The products overlap in the daily dosing frequency. However, they differ in every other product characteristic as shown by the following: dosage form (cream compared to tablet), strength (10 grams compared to 45 mg, 90 mg and 135 mg), and indication (burns compared to acne). In addition, the strengths of Solodyn do not overlap with the order amounts for Silvadene (45, 90, and 120 mg compared to 20, 50, 85, 400 and 1000 grams). As the products differ in multiple products characteristics, DMETS believes the possibility for confusion to be minimal.
7. Razadyne may look similar to Solodyn when scripted. Razadyne contains galantamine hydrobromide in tablet, capsule and oral solution forms for the treatment of Alzheimer disease. For the immediate-release product, the recommended dosing is 16 to 32 mg per day, administered twice daily. The extended-release product of Razadyne ER is dosed at 16 to 24 mg per day. The orthographic similarities stem from the shared "dyn" with similar placement and the possibility for the "z" of Razadyne to resemble the "l" of Solodyn when surrounded by vowels that appear similar when scripted ("a" and "o").



The products share the tablet dosage form and oral route of administration. The controlled release Razadyne product shares the daily dosing frequency, but the prescription should indicate "ER" that will further differentiate the name. Furthermore, Razadyne strengths do not overlap (4 mg, 8 mg, 12 mg, 16 mg and 24 mg) when compared to Solodyn (45 mg, 90 mg and 135 mg). As the products differ in multiple product characteristics, DMETS believes the possibility for confusion to be minimal.

8. Zolpidem may sound similar to Solodyn when scripted. Zolpidem is the active ingredient of Ambien, a product used in the short-term treatment of insomnia. Zolpidem is available as an immediate release tablet form of 5 mg and 10 mg and controlled release of 6.25 mg and 12.5 mg to be dosed daily before bedtime. A verbal study participant identified the proposed name as "Zoliden", which is phonetically similar to Zolpidem. The phonetic similarities stem from the shared three syllables, similar sounding introductory and concluding syllables (ōl and dīn). However, prominence given in speech to the central syllable of "pi" in Zolpidem should help to alleviate confusion. The drug products share the characteristics of dosage form (tablet), route of administration (oral) and frequency of dosing (daily). However, they differ in the key

characteristic of strength (5 mg, 6.25 mg, 10 mg and 12.5 mg compared to 45 mg, 90 mg and 135 mg). As the similarity is in the phonetic similarities, this would involve confusion on a verbal order. Each drug product has multiple strengths, thus this would be required information to complete the order and each of these strengths are distinct in speech. In addition, the prescriber may indicate "CR" on the verbal order that will further provide another method of product differentiation. As the strengths differ, DMETS believes the possibility for confusion to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS has reviewed the container label, carton and insert labeling and have definitive comments of the insert labeling. However, any recommendations for these container and carton labels would be guidelines as DMETS is unsure of the actual label presentation by what was submitted by the sponsor.

A. GENERAL COMMENT

1. We note the established name reflects "modified release" to describe the dosage form. The term modified-release is not a dosage formulation recognized by the US Pharmacopeia (USP). Revise to read as either "extended-release" or "delayed-release"; whichever is appropriate for this dosage form. For input on which designation is most appropriate, contact Guiragos Poochikian of the LNC.
- 2.



B. CONTAINER LABEL (100 Count)

1. The product is available in several strengths and dosage forms. We are unable to determine from the black and white samples provided by the Division whether the different strengths and dosage forms are clearly differentiated from one another. Please revise to include a contrasting color, boxing, or some other means.
2. The current presentation of the strength of minocycline based on the hydrochloride salt is incomplete and confusing. In addition, revise the proprietary name, established name and strength adjacent to each other for ease of identification. We recommend expression of the strength and name presentation in one the following formats (see below and page 11):

- a. Solodyn
(Minocycline Extended-release Tablets)
45 mg
- b. Solodyn
(Minocycline Hydrochloride Extended-release Tablets)
45 mg*

*Each tablet contains minocycline hydrochloride equivalent to 45 mg of minocycline hydrochloride.

c. Solodyn
(Minocycline Hydrochloride Extended-release Tablets)
equivalent to 45 mg of Minocycline Hydrochloride

Of note, DMETS prefers the first example (“a”) since this nomenclature is consistent with USP recommendations on the “labeling of salts of drugs.” Additionally, the insert labeling should be revised to clarify the dosing as well.

3. Relocate the “Rx only statement” to the bottom third of the label to allow for increased prominence of the critical information of product strength and name.
4. Relocate the net quantity statement away from the product strength. The current presentation of the net quantity has increased prominence over the strength and may result in confusion with the product strength.

C. CARTON LABEL

1. See Comments B 1 through 4.

D. SAMPLE BLISTER LABEL

1. See Comment B 2.
2. As currently presented, it appears top section of the blister pack does not include the product strength. Please revise.
3. If the package configuration is more than a single blister cell, please assure each blister cell is labeled with the product name and strength.
4. Revise the established name to read “Tablet” rather than “Tablets”, since each blister represents one tablet.

E. SAMPLE DUMPBIN CONTAINER

1. See Comments B 1 through 4.
2. Please delete the bolded after the notation of 45 mg. This presentation misleads the reader to assume there is 45 in the container.

F. INSERT LABELING

1. See General Comment A and B 2 above.
2. As this appears to be an extended-release tablet, DMETS assumes the tablet can not be halved/broken. However, please state whether the tablet can be halved or broken and ingested in the “Dosage and Administration” and “Information for the patients” sections of the insert labeling. Since the tablet strengths are multiples of each other, patients and practitioners may question if halving the tablet is possible to save money. In addition, patients may question if ingestion is possible if the tablets break.
3. In reference to the table, there is a trailing zero in the final total dose (7.0). Please delete this trailing zero. Trailing zeros often result in error as the decimal is overlooked. As evidenced by our post-marketing surveillance, the use of trailing zeros could potentially result in a ten-fold medication dose error. Although, it is unlikely that a ten-fold medication dosing error would

occur, since the product is packaged in the required size and volume for administration, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 12) of 2000 USP, which states, "...to minimize the possibility of errors in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." In addition, the use of trailing zeros is specifically listed as in the list of dangerous abbreviations, acronyms, and symbols in the National Patient Safety Goal 2 of The Joint Commission of Accreditation of Healthcare Organizations (2006). Lastly, safety groups such as ISMP, also list this on their dangerous abbreviations and dose designations.

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Appendix A. DMETS prescription study results for Solodyn

Inpatient	Outpatient	Voice
Solodyn	Solodyne	Solidex
	Solodyne	Soloden (soledan)
	Solodyne	Soliden
		silvidin
Solodyn		Soladyn
Solodyn	Solodyne	Zoliden
	Solodyne	Silavden
Solodyn	Solodyne	Sulvaden
Solodyn	Solodyne	Solidan
Solodyn	Solodyne	Solodyn
	Solodyne	Solodyne
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this page is the manifestation of the electronic signature.**

/s/

Kimberly Culley-Pedersen
1/6/2006 12:05:42 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/6/2006 12:50:27 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
1/6/2006 01:10:53 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/6/2006 03:00:33 PM
DRUG SAFETY OFFICE REVIEWER



ORIGINAL

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DEC 23 2005

CDER/CDER RECEIVED

DEC 28 2005

December 22, 2005

NDA 50-808-02

Stanka Kukich, M.D., Acting Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Minor Amendment CDER White Oak DR1
Worldwide Safety Assessment
Spermatogenesis Final Study Report

Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release —
45 mg, 90 mg and 135 mg

N 209(02)
ORIG AMENDMENT

Dear Dr. Wilkin:

Reference is made to NDA 50-808, SOLODYN™, Modified Release — submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Reference is also made to the September 13, 2005 FDA faxed filing communication, providing Clinical and Statistical comments to the original NDA (eCTD) filing for this product in which a Worldwide Safety Assessment for all minocycline formulations was requested. On October 4, 2005, Medicis submitted a request for guidance on this issue to ensure that the information we provide is in line with the Agency's needs. Based on the response received on October 17, 2005, Medicis hereby submits the requested information in section M1.11.2 of the eCTD.

Also Included in this amendment is the final study report for study MP-0104-13 entitled *An Open-Label Phase I Study to Examine the Effects of Minocycline on Spermatogenesis in Human Males*. The final study report is included in section M5.3.4.1 of the eCTD.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fwv

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

Curtis, Felecia

From: Willy Brondum [wbrondum@medicis.com]
Sent: Tuesday, November 29, 2005 1:34 PM
To: Curtis, Felecia
Cc: Michelle Wells
Subject: NDA 50-808
Signed By: wbrondum@medicis.com



111605 NDA
-808 Minor Amendm

Dear Felecia,

We are having some difficulty making an electronic copy of the full Minor Amendment eCTD submission dated November 16, 2005. However, while we are sorting this out, Fran thought it would be most helpful if you at least had the detailed cover letter for the submission.

We appreciate your patience. Please do not hesitate to call me if I can be of further assistance.

Regards,

Willy Brondum
Regulatory Affairs Manager, CMC
Medicis Pharmaceutical Corporation
8125 N. Hayden Rd.
Scottsdale, AZ 85258
602-667-3907 direct phone
602-778-6107 fax



November 16, 2005

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

Minor Amendment

**Re: NDA 50-808 SOLODYN™ (Minocycline Hydrochloride) Modified Release _____
45 mg, 90 mg and 135 mg**

Dear Dr. Wilkin:

Reference is made to NDA 50-808, SOLODYN™, Modified Release _____ submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

In accordance with 21 CFR 314.50 (5)(vi)(b), enclosed within Section M5.3.5 of the eCTD please find the 120-Day Safety Update for this product. Included in this 120-Day Safety Update is a report of adverse events and concomitant medications for all subjects, including tables and listings, continuing to receive Solodyn® Modified Release _____ in conjunction with enrollment in study MP-0104-07 entitled "An Open-Label Safety Study of _____: Minocycline for Treatment of Moderate to Severe Acne" and Study MP-0104-13 entitled "An Open-Label Phase I Study to Examine the Effects of Minocycline on Spermatogenesis in Human Males". All data reported in this update reflects information on all subjects through July 31, 2005.

Reference is also made to the September 13, 2005 FDA faxed filing communication, providing Clinical and Statistical comments to the original NDA (eCTD) filing for this product.

This amendment includes responses to the September 13, 2005 filing communication as well as the 120-Day Safety Update for the NDA.

FDA Filing Communication, September 13, 2005

Below please find FDA's comments in *italics* followed by Medicis' responses.

CLINICAL

FDA Comment:

Results from the two spermatogenesis studies, MP-0104-16 and MP-0104-13, show that minocycline therapy appears to have an effect on spermatogenesis. Considering that minocycline may be chronically used by patients (mostly by younger patients) to treat their acne, these results are concerning. For any ongoing studies, the Agency reiterates that

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

patients who show effects on spermatogenesis at day 156 should be followed until clinical resolution.

Action Item

Please submit a complete study report of the spermatogenesis studies, MP-0104-16 and MP-0104-13, to the NDA application as soon as possible.

Current labeling of minocycline and the proposed labeling includes the observation that minocycline has been shown to affect sperm counts and motility in rats. Human data on the effect on spermatogenesis is very limited.

The final report for study MP-0104-16 was submitted with NDA 50-808 submitted June 30, 2005 filed July 7, 2005. As communicated to the Agency in our correspondence dated September 2, 2005, study MP-0104-13 has been discontinued. The study was being conducted at the MDS facility in New Orleans, Louisiana, and because of the devastation caused by Hurricane Katrina, the site has been closed until further notice and the subjects have been scattered throughout the region. It now appears to be impossible to locate subjects to obtain the needed samples in a timely manner according to the protocol. At the time the study was discontinued, 14 subjects had data available through Day 156, the scheduled study completion date. End of study files are incomplete for the 14 subjects due to the premature closure of the study and the inability to retrieve the final case report forms. We will, of course, work with the site, to collect any additional data that becomes available once the site is able to reopen. Medicis will submit a final report to the Agency prior to December 31, 2005.

FDA Comment:

Follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis do not appear to be available in the submission.

Action Item

Please indicate where in the submission are the follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis. Please provide such data if not yet submitted.

Study MP-0104-16 was designed to provide only one semen sample for analysis. Medicis has completed follow-up of the two subjects who had analyses indicating azospermia. The endocrine summary for subject 57-018 (treated with minocycline) is appended to the study report found in Section M5.3.4.2. Evaluation by a medical specialist diagnosed the subject with idiopathic azospermia. Subject 54-011 (treated with placebo), after questioning by the site, admitted to having a vasectomy and was actually not eligible for the enrollment in the study. A copy of the letter to the IRB documenting reporting of the vasectomy is appended to the study report found in Section M5.3.4.2.

As stated above, Medicis' ability to provide further follow-up on MP-0104-13 is unclear at this time.

Medicis has convened a panel of male reproductive specialists to review and comment on the existing data both in the literature and developed by Medicis. In brief, the panel does not believe that MP-0104-13 and MP-0104-16 are instructive regarding the effect of minocycline on sperm and are recommending that a definitive study be undertaken. Medicis is including details of the panel's findings in this submission as part of the 120-Day Safety Update. With

the aid of this expert panel, Medicis has developed a definitive study to investigate the effect, if any, on sperm by the tetracycline-class of antibiotics, including this formulation of minocycline. In addition to the comments for the expert panel, the design of the study has incorporated the comments provided by the Reproductive and Urologic Drug Products via the Dermatologic Division provided on February 2, 2005. Medicis commits to conduct a study to better understand the affects of the tetracycline-class on sperm and plans to submit the protocol for FDA comment very soon.

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[Redacted]

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STATISTICAL

FDA Comment

SAS transport datasets containing the Evaluator's Global Severity Assessment (Inflammatory and Noninflammatory Lesions) and a copy of the annotated (blank) CRF containing the pages where evaluations of this endpoint were recorded for studies MP-0104-04 and MP-0104-05 were not submitted to the application.

Action Item

Submit SAS transport datasets containing the Evaluator's Global Severity Assessment (Inflammatory and Noninflammatory Lesions) and a copy of the annotated (blank) CRF containing the pages where evaluations of this endpoint were recorded for studies MP-0104-04 and MP-0104-05.

The requested Annotated Case Report Forms and SAS datasets are included within section M5.3.5.1 of the eCTD.

FDA Comment

Analysis datasets for Studies MP-0104-04 and MP-0104-05 that include derived variables were not submitted to the application.

Action Item

Submit analysis datasets for studies MP-0104-04 and MP-0104-05 that include the following derived variables: inflammatory lesion count, non-inflammatory lesion count, change from baseline in inflammatory lesions, change from baseline in non-inflammatory lesions, percent change from baseline in inflammatory lesions, percent change from baseline in non-inflammatory lesions, and success on the Evaluator's Global Severity Assessment (Inflammatory Lesions Only) (Clear/Almost clear), along with the variables for treatment site, analysis center, race, age, gender, ITT status, and per protocol status. The primary endpoints (percent change in inflammatory lesions and success on the global assessment) should be presented as both observed cases and imputed for missing data (LOCF).

The requested analysis data sets are included within section M5.3.5.1 of the eCTD.

FDA Comment

Pages of Zar (1984, Biostatistical Analysis) relevant to the test for skewness of the distribution of percent change were not submitted with the application.

Action Item

Submit a copy of the pages of Zar (1984, Biostatistical Analysis) relevant to the test for skewness of the distribution of percent change.

The requested pages of Zar are included Section M5.4.

FDA Comment

Background information and details about the interactive voice-recognition system (IVRS) and how the system generates randomization assignments were not submitted to the application.

Action Item

Provide additional background information and details about the interactive voice-recognition system (IVRS) and how the system generates randomization assignments.

Background information regarding the interactive voice-recognition system (IVRS) for Studies MP-0104-01, MP-0104-04 and MP-0104-05 has been added to Section M5.3.5.1.

Also as part of this amendment, in order to expedite the proprietary name approval process and facilitate review, Medicis Pharmaceutical Corporation hereby submits the following proprietary name for Minocycline HCl Modified Release Caplets for consideration by the Division of Dermatologic and Dental Drug Products and Division of Medication Errors and Technical Support (DMETS):

SOLODYN™ (minocycline HCl) Modified Release 45, 90 and 135 mg

Should SOLODYN™ not be accepted, the following names are submitted as alternates:

_____ (first alternate)
_____ (second alternate)

SOLODYN™ (Minocycline hydrochloride) Modified Release
Minor Amendment

NDA 50-808
November 2005

Copies of the revised container labeling and the package insert will be submitted under separate cover to the NDA eCTD once the proprietary name approval process has been completed.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

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October 17, 2005

NDA 50-808

Clinical Response to Sponsor facsimile dated 10/3/05 (Request for Guidance)

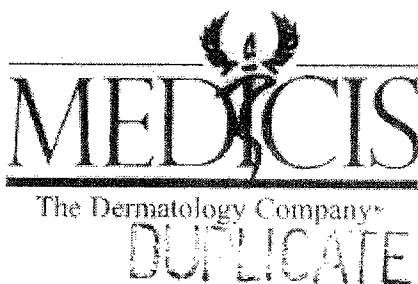
- 1) We need worldwide information on safety assessment for Medicis' formulations as available, but a literature search and any available data on other formulations of minocycline would be relevant information and a best effort should be made to address.
- 2) Focus on adverse events with the treatment of acne is recommended. However, relevant safety information regarding adverse events for other indications should be included.
- 3) An integrated summary of the literature is requested. Please include copies of any literature that is referenced, in addition to citation.
- 4) The pertinent time frame should include at least the last 5 years. However, significant safety information from previous to that time frame should also be included as minocycline is not a very new drug and pertinent AEs from earlier may be relevant in the context of new AEs observed or for AEs not reported recently due to their already been reported.

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/s/

Felicia Curtis
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CSO



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OCT 19 2005
CDER/CDER

October 14, 2005

Jonathan K. Wilkin, M.D., Director
Food and Drug Administration
Division of Dermatologic and Dental Products (HFD 540)
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

ORIG AMENDMENT
N-000-(BC)

Request for Guidance

Re: NDA 50-808 SOLODYN® (Minocycline Hydrochloride) Modified Release
45 mg, 90 mg and 135 mg

Dear Dr. Wilkin:

Reference is made to NDA 50-808, SOLODYN®, Modified Release , submitted on June 30, 2005. Further reference is made to the August 19, 2005 telephone contact with Felicia Curtis in which she requested an official submission be filed to the Solodyn application.

Medicis respectfully requests guidance regarding the filing requirements for changes to the proposed packaging sizes for Solodyn Modified Release . A detailed summary and supporting documentation is enclosed.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

dms

Best Possible Copy

REQUEST FOR CONSULTATION

TO (Division/Office):

Kathleen Uhl
HFD-020
RKW2 RM1031

FROM:

Felecia Curtis, PM
Division of Dermatology and Dental Products
White Oak Bldg

DATE
October 13, 2005

IND NO.

NDA NO. 50-808

TYPE OF DOCUMENT: New NDA)

DATE OF DOCUMENT:
June 30, 2005

NAME OF DRUG
Solodyn (Minocycline
Hydrochloride)

PRIORITY CONSIDERATION:
Target date 2/7/06

CLASSIFICATION OF DRUG: 3S

DESIRED COMPLETION DATE:
January 15, 2006

NAME OF FIRM: Medicis

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COM COMMENTS / SPECIAL INSTRUCTIONS:

a) Please provide comments regarding the Pregnancy Registry Protocol for Solodyn (Minocycline Hydrochloride).

b) Please review and comment on the pregnancy category for the indication of acne vulgaris.

If you have any questions, please contact me at 301-796-0877 or email curtisf@cdcr.fda.gov or Bindi Nikhar, M.D, at 301-796-0961. Thank you.

PDUFA DATE: 5/8/2006

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 50-808

HFD-540/Division File

HFD-540/Felecia Curtis

HFD-540/Reviewers and Team Leaders

SIGNATURE OF REQUESTER
Felecia Curtis

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

26 Page(s) Withheld

 Trade Secret / Confidential

 6 Draft Labeling

 Deliberative Process

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/s/

Felicia Curtis
10/13/2005 02:02:20 PM



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NEW CORRESP
N-000-(e)

DUPLICATE

October 3, 2005

Jonathan K. Wilkin, M.D., Director
Food and Drug Administration
Division of Dermatologic and Dental Products (HFD 540)
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Corporate 2, Room N214
Rockville, MD 20850

Request for Guidance

Re: **NDA 50-808 SOLODYN® (Minocycline Hydrochloride) Modified Release** _____
45 mg, 90 mg and 135 mg

Dear Dr. Wilkin:

Reference is made to NDA 50-808, SOLODYN®, Modified Release _____, submitted on June 30, 2005 with a User Fee Receipt Date of July 8, 2005. Further reference is made to the September 13, 2005 FDA faxed filing communication, providing Clinical and Statistical comments to the original NDA (eCTD) filing for this product.

Medicis respectfully requests guidance regarding the submission of a Worldwide Safety Assessment as requested in the September 13, 2005 filing communication.

Below please find FDA's comments in *italics* followed by Medicis' questions.

FDA Comment

*Worldwide safety assessment for all minocycline formulations was not submitted to the application.
Please submit a worldwide safety assessment for all minocycline formulations*

Medicis Questions:

1. Does the Agency's request require that all information on all worldwide formulations of minocycline be submitted, or is the Agency looking for worldwide information for Medicis' minocycline formulations exclusively? Medicis' current minocycline formulations include:

- ANDA 65-131 Dynacin (minocycline HCl) Tablets 50, 75 and 100 mg
- ANDA 63-066 Dynacin (minocycline HCl) Capsules 50 mg
- ANDA 63-067 Dynacin (minocycline HCl) Capsules 75 and 100 mg

2. Does the Agency's request require that all information on all indications of minocycline be submitted, or is the Agency looking for worldwide information about minocycline use for acne only?

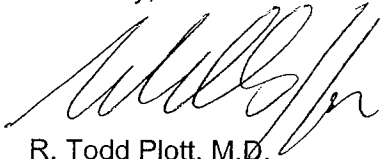
3. Does the Agency wish to receive the results for a worldwide literature search with articles, or a report with integrated analysis of the worldwide literature?

4. Medicis intends to use the last three years as a time frame for the search criteria of the worldwide safety assessment, is this acceptable to the Agency?

Medicis commits to submitting responses to all questions on the September 13, 2005 filing correspondence by mid-October. The Worldwide Safety Assessment will be submitted as soon as it is completed and becomes available, following FDA's guidance on Medicis' questions included in this request.

Should you have questions or need additional clarification, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs

fww

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-808

Medicis

Attention: R. Todd Plott, M.D.

Vice President, Clinical Research & Regulatory Affairs

8125 North Hayden Road

Scottsdale, AZ 85258

Dear Dr. Plott:

Please refer to your June 30, 2005, new drug application (NDA), received July 8, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Solodyn (minocycline hydrochloride) Modified Release [REDACTED] 45 mg, 90 mg, and [REDACTED] mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 6, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

CLINICAL

1. Results from the two spermatogenesis studies, MP-0104-16 and MP-0104-13, show that minocycline therapy appears to have an effect on spermatogenesis. Considering that minocycline may be chronically used by patients (mostly by younger patients) to treat their acne, these results are concerning. For any ongoing studies, the Agency reiterates that patients who show effects on spermatogenesis at day 156 should be followed until clinical resolution.
2. Follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis do not appear to be available in the submission.
3. Draft labeling for minocycline modified release [REDACTED] as currently worded with regard to the risk versus benefit in the treatment of acne vulgaris, is not adequate.
4. Draft labeling in the Pregnancy Category/Nursing Mothers/Warnings sections of the minocycline modified release (MR) [REDACTED] is not in line with known teratogenic adverse effects of minocycline.
5. Adverse events in the draft minocycline label are not in a tabular form.
6. Worldwide safety assessment for all minocycline formulations was not submitted to the application.

7. Photographs of subjects before and after treatment were not submitted to the application..

STATISTICAL

1. SAS transport datasets containing the Evaluator's Global Severity Assessment (Inflammatory and Noninflammatory Lesions) and a copy of the annotated (blank) CRF containing the pages where evaluations of this endpoint were recorded for Studies MP-0104-04 and MP-0104-05 were not submitted to the application.
2. Analysis datasets for Studies MP-0104-04 and MP-0104-05 that include derived variables were not submitted to the application.
3. Pages of Zar (1984, *Biostatistical Analysis*) relevant to the test for skewness of the distribution of percent change were not submitted with the application.
4. Background information and details about the interactive voice-recognition system (IVRS) and how the system generates randomization assignments were not submitted to the application.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

CLINICAL

1. Please submit a complete study report of the spermatogenesis studies, MP-0104-16 and MP-0104-13, to the NDA application as soon as possible.
2. Please indicate where in the submission are the follow-up results on any affected subjects demonstrating return to baseline post-therapy for studies MP-0104-16 and MP-0104-13 with regard to semen analysis. Please provide such data if not yet submitted.
3. Please submit revised draft labeling for minocycline modified release caplets in line with the risk versus benefit in the treatment of acne vulgaris.
4. Please reconsider draft Pregnancy Category/Nursing Mothers/Warnings sections of the minocycline modified release (MR) Caplets in line with the known teratogenic adverse effects of minocycline.
5. Please list all adverse events in the minocycline label in a tabular form.
6. Please submit a worldwide safety assessment for all minocycline formulations.
7. Please submit photographs of subjects before and after treatment if available.

STATISTICAL

1. Submit SAS transport datasets containing the Evaluator's Global Severity Assessment (Inflammatory and Noninflammatory Lesions) and a copy of the annotated (blank) CRF containing the pages where evaluations of this endpoint were recorded for Studies MP-0104-04 and MP-0104-05.
2. Submit analysis datasets for Studies MP-0104-04 and MP-0104-05 that include the following derived variables: inflammatory lesion count, non-inflammatory lesion count, change from baseline in inflammatory lesions, change from baseline in non-inflammatory lesions, percent change from baseline in inflammatory lesions, percent change from baseline in non-inflammatory lesions, and success on the Evaluator's Global Severity Assessment (Inflammatory Lesions Only) (Clear/Almost clear), along with the variables for treatment, site, analysis center, race, age, gender, ITT status, and per protocol status. The primary endpoints (percent change in inflammatory lesions and success on the global assessment) should be presented as both observed cases and imputed for missing data (LOCF).
3. Submit a copy of the pages of Zar (1984, *Biostatistical Analysis*) relevant to the test for skewness of the distribution of percent change.
4. Provide additional background information and details about the interactive voice-recognition system (IVRS) and how the system generates randomization assignments.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Felecia Curtis, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.

Director

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin
9/13/2005 06:44:53 PM



RECEIVED
SEP 07 2005
CDR / ODER

September 2, 2005

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Products (HFD-540)
Center of Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

RECEIVED
SEP 08 2005
MEGA / CDER
AL 022(BM)

RE: **NDA 50-808 SOLODYN® (Minocycline Hydrochloride)**
Modified Release 45mg, 90mg and 135 mg

Dear Dr. Wilkin:

ORIG AMENDMENT

Reference is made to NDA 50-808, submitted on June 30, 2005, with a User Fee Receipt Date of July 8, 2005. Further reference is made to the related IND 65,398, in which the protocol referenced below was filed on October 26, 2004.

The purpose of this letter is to inform the Agency that Medicis Pharmaceutical Corp. has discontinued study MP-0104-13, entitled *An Open-Label Phase I Study to Examine the Effects of Minocycline on Spermatogenesis in Human Males*. This single center study was being conducted at in . We have been advised the facility has been destroyed by Hurricane Katrina. At this time the site is not available for inspection and the date to re-open the facility, if ever, is undetermined. If the facility does re-open, it is not expected that the source data and CRFs that had not been collected will be intact. Additionally, finding the subjects who have not yet completed the study could be very difficult, if not impossible. In fact, many may be lost to follow-up for the purposes of the study, as the window around the study visits is +/- 2 days for visits occurring while on minocycline treatment (through Day 84) and +/-7 for post treatment visits (Day 112 and Day 156). Therefore, there seems little alternative but to close this trial with the existing data in-hand.

A total of 30 healthy male subjects (to complete 24) were to be enrolled in the study. As of August 30, 2005 29 subjects had been enrolled. The table below indicates the data that have been collected.

	Through Baseline	Through Day 28	Through Day 56	Through Day 84	Through Day 112	Through Day 156
# of subjects	26	23	22	15	15	15

DUPLICATE

A total of 116 plasma samples for analysis of LH, FSH, testosterone and minocycline have been received from 29 subjects, 11 subjects with samples through Day 156, 12 subjects with samples through Day 84, 5 subjects with samples through Day 56 and 1 subject with samples from Day 1 only.

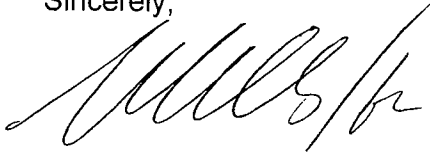
Information from the study will be included in the 4-month safety update to the NDA to be submitted November 9, 2005. All data collected will be analyzed and a final report will be prepared and submitted to the Agency. The final study report should be submitted prior to year-end.

When, and if, it becomes possible for us to return to the study center, we will recover any data that remains at the site, and we will amend the final report accordingly. A note to file noting the disposition of subjects and data will be included in the final report.

Medicis is committed to fully investigating the effect, if any, of minocycline on spermatogenesis. Medicis plans further discussions with experts in the field to evaluate existing data and plan future definitive studies of this matter.

Should you have any questions or need additional information please do not hesitate to contact Michelle Wells, RAC, Associate Director of Regulatory Affairs, at 602-808-3851 or by fax at 602-778-6051.

Sincerely,

A handwritten signature in black ink, appearing to read 'R. Todd Plott, MD'. The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

R. Todd Plott, MD
Vice President, Clinical Research and Regulatory Affairs

**Appears This Way
On Original**



August 26, 2005

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

**MINOR
AMENDMENT**

**Re: NDA 50-808 SOLODYN® (Minocycline Hydrochloride) Modified Release _____
45 mg, 90 mg and 135 mg**

Dear Dr. Wilkin:

Reference is made to NDA 50-808, SOLODYN®, Modified Release _____ submitted on June 30, 2005. Reference is also made to IND 65,398 submitted on July 12, 2002 in support of this NDA.

Further reference is made to the August 22, 2005 teleconference between FDA representatives, Felecia Curtis, Regulatory Project Manager, Norman See, Ph.D., Pharmacology Reviewer and Michelle Wells, Associate Director, Regulatory Affairs, Medicis Pharmaceutical Corp., during which the Agency requested updates regarding the Chronic Toxicology Study referenced in this NDA.

Below please find FDA's comments in *italics* followed by Medicis' responses to the August 22, 2005 FDA fax.

FDA Comment:

The chronic toxicology study will not be considered to be a filing issue, provided the initial submission to the NDA contains a protocol for the chronic toxicology study, a current interim report or update concerning that study, appropriate dose-ranging data to support the selection of dosages used, and a clear commitment to submit data from that study within a specific time frame. The sponsor will be expected to have initiated a suitable study prior to submission of the NDA.

Medicis Response:

In accordance with our previously made commitment, an interim report, which includes a copy of the final protocol for this study is enclosed within this amendment for review. Information regarding appropriate dose-ranging data to support the selection of dosages used was submitted in the original NDA filing for this product within the eCTD in section M4-2-3-2, repeat dose toxicity. Please note Medicis commits to submitting the Final Study Report no later than April 15, 2006

Medicis also submitted a copy of the final protocol for -450012: *A 9-Month Oral (Gavage) Study In Cynomolgus Monkeys*, to IND 65,398 as an Amendment (S-0030) on February 23, 2005.

This protocol was submitted in response to the FDA reviewer's comments on May 28, 2003, in which a chronic toxicology study update, appropriate dose-ranging data and a clear commitment to submit data from that study were requested. At the time Medicis was granted a waiver to allow the filing of the NDA for this product to include an interim report on the on-going chronic study with knowledge that the final report would be submitted when the study is complete.

Should you have questions or need additional information, please do not hesitate to contact Michelle Wells, RAC, Associate Director, Regulatory Affairs at 602-808-3851 or by fax at 602-778-6051.

Sincerely,



R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
Medicis Pharmaceutical Corp.

fww

Appears This Way
On Original

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM: Felecia Curtis PM/

HFD-540, Derm and Dental

Ext. 72043

DATE August 24, 2005	IND NO.	NDA NO. 50-808	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 30, 2005
-------------------------	---------	-------------------	-----------------------------	-----------------------------------

NAME OF DRUG Solodyn (Minocycline Hydrochloride)	PRIORITY CONSIDERATION Target date 2/7/06	CLASSIFICATION OF DRUG 3s	DESIRED COMPLETION DATE January 6, 2006
--	--	------------------------------	--

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): see below explanation |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

I the division would like ODS to focus on Minocycline use for the acne indication. For the other indications, the focus could be on the following:
1) birth defects; 2) hepatotoxicity; 3) skin adverse effects (Stevens- Johnson syndrome, phototoxicity, etc); 4) lupus-related AEs & any other AEs leading to death or hospitalization in all indications.

COMMENTS / SPECIAL INSTRUCTIONS:

PDUFA DATE: 5/8/06

CC: Archival IND/NDA 50-808

HFD-540/Division File

HFD-540/Felecia Curtis

HFD-540/Reviewers and Team Leaders

SIGNATURE OF REQUESTER

Felecia Curtis, PM

METHOD OF DELIVERY (Check one)

MAIL

EMAIL / DFS
 HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
8/24/2005 04:08:25 PM

REQUEST FOR CONSULTATION

TO (Office/Division): Division of Drug Marketing, Advertising
& Communications, HFD-42 PKLN Room 19B04

FROM (Name, Office/Division, and Phone Number of Requestor): Felicia
Curtis, Regulatory Project Manager, DDDDP, 301-827-
2043

DATE 08/22/2005	IND NO.	NDA NO. 50-808	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT 06/30/2005
NAME OF DRUG Solodyn (minocycline hydrochloride) Modified Release		PRIORITY CONSIDERATION Target date 02/07/2006	CLASSIFICATION OF DRUG 3S	DESIRED COMPLETION DATE 01/15/2006

NAME OF FIRM: Medicis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|---|---|--|
| <input checked="" type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|---|--|

II. BIOMETRICS

- | | |
|--|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please find attached the PI, carton and container labels for the above NDA for your review.

SIGNATURE OF REQUESTOR
Felicia Curtis 301-827-2043

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

26 Page(s) Withheld

 Trade Secret / Confidential

 b Draft Labeling

 Deliberative Process

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this page is the manifestation of the electronic signature.**

/s/

Maria Anderson
8/22/2005 09:59:29 AM
For Felicia Curtis

MEMORANDUM OF TELECON

DATE: August 22, 2005 10:05 AM

APPLICATION NUMBER: NDA 50-808

DRUG PRODUCT: Solodyn (Minocycline Hydrochloride)

BETWEEN:

Division of Dermatologic and Dental Drug Products, HFD-540

Norman See, Ph.D./Pharmacology Reviewer, DDDDP, HFD-540

Felecia Curtis, Regulatory Project Manager

AND

Attendees via teleconference:

Michelle Wells, Regulatory Affairs Consultant for Medicis

SUBJECT: NDA 50-808

This teleconference was initiated by the Agency to request information from Medicis Pharmaceutical. During a meeting on May 28, 2003, Medicis requested "a waiver to allow the filing of the NDA to include an interim report of the on-going chronic study with knowledge that the final report will be submitted when the study is complete". It was agreed that the chronic toxicology study would not be considered to be a filing issue, provided the initial submission to the NDA contained "a protocol for the chronic toxicology study, a current interim report or update concerning that study, appropriate dose-ranging data to support the selection of dosages used, and a clear commitment to submit data from that study within a specific time frame". The initial examination of NDA 50-808 did not locate the protocol, current interim report, or anticipated date of submission for the 39-week monkey study that is stated in the NDA to be "ongoing".

The Agency requested that the sponsor either indicate where these materials are located in the NDA or, if necessary, submit these materials.

The sponsor agreed to submit information requested in timely manner to expedite the review process.

The conversation ended amicably.

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/s/

Felicia Curtis
8/22/2005 11:51:18 AM
CSO

Norman See
8/22/2005 11:56:14 AM
PHARMACOLOGIST

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Monday, August 22, 2005 4:44 PM
To: Felecia Curtis (E-mail); Norman A. See PhD (E-mail)
Subject: RE: NDA 50-808
Signed By: mwells@medicis.com

I'm resending due to a delivery failure.

> -----Original Message-----

> From: Michelle Wells
> Sent: Monday, August 22, 2005 1:33 PM
> To: Felecia Curtis (E-mail); Norman A. See PhD (E-mail)
> Subject: NDA 50-808

>
> The Final Protocol for ~~XXXX~~-450012: A 9-Month Oral (Gavage) Study In
> Cynomolgus Monkeys was last submitted in S-0030, filed on 2/23/05 to
> IND 65,398.

>
> We are expecting an interim report to be available to us later this
> week (Thursday noon), which we will submit to our external vendor for
> conversion to a CTD amendment. I have not had confirmation of the
> timing for that submission yet, but I'm hoping it will be next week.
> However, I can submit the protocol and interim report electronically
> as soon as they come in, with the formal submission to follow shortly
> thereafter.

>
> Please don't hesitate to contact me anytime with questions. Feel free
> to use my cellphone number when you have other attendees (more of a
> guarantee that you'll reach me directly).

>
> I'll keep you posted on the status of the amendment.

>
> Regards,
> Michelle

>
> Michelle Ann Wells, RAC
> Associate Director, Regulatory Affairs
> Medicis Pharmaceutical Corporation
> 8125 North Hayden Road
> Scottsdale AZ 85258

>

> Main: 602 808 8800

> Direct: 602 808 3851

> Fax: 602 778 6051

Cell: 480 221 9968

>

> mwells@medicis.com <mailto:mwells@medicis.com>

>

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Wednesday, August 17, 2005 11:14 AM
To: Felecia Curtis (E-mail)
Subject: NDA 50-808
Signed By: mwells@medicis.com

Felecia -

I have your request for the chronic tox studies protocol and reports or interim reports.

I'll figure that out as quickly as possible and will get right back to you.

Regards,
Michelle

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800
Direct: 602 808 3851
Fax: 602 778 6051
Cell: 480 221 9968

mwells@medicis.com <<mailto:mwells@medicis.com>>

Curtis, Felecia

From: Kozma-Fornaro, Mary J
Sent: Friday, August 12, 2005 1:03 PM
To: Curtis, Felecia
Cc: Anderson, Maria M (ODEIII); Jain, Shalini
Subject: RE: Solodyn NDA 50-808

Save this for the action package. Bindi is using Risk Management in a very broad sense. We can request an updated AE report from ODS....but it appears Markham wants the worldwide report from Medicis. I am not certain if we told them this at the pre NDA meeting.

120 days after submission of the NDA they have to give a safety update but that generally is on the study conducted. We may have to address the updated worldwide request in filing. MJ

-----Original Message-----

From: Curtis, Felecia
Sent: Friday, August 12, 2005 12:45 PM
To: Kozma-Fornaro, Mary J
Subject: FW: Solodyn NDA 50-808

Relating to RMP.

-----Original Message-----

From: Nikhar, Bindi
Sent: Friday, August 12, 2005 11:17 AM
To: Curtis, Felecia; Luke, Markham C
Subject: Solodyn NDA 50-808

Felicia,

ODS (Marilyn Pitts) had done a review for Minocycline on 4/21/2004.

Markham,

Should we consult them for an update from the previous review or shall we ask them informally for an update? In April 2004, they had focused on AEs related to the acne indication only, and out of the 4,529 AEs reported, 662 were for the acne indication (including 6 deaths). Marilyn suggested we add a post-marketing section to include serious outcome when minocycline is used to treat acne.

The sponsor should really provide us with an updated worldwide safety on Minocycline and a Risk Management program soon too. Not providing us with a worldwide safety report is almost a reason to refuse to file this NDA.

Thanks,

Bindi

Appears This Way
On Original

Curtis, Felecia

From: Michelle Wells [mwells@medicis.com]
Sent: Friday, August 12, 2005 12:36 PM
To: Felecia Curtis (E-mail)
Subject: Here's another try

This is what I "see" on my end, when I scroll down to the m5 section.

I highlighted in bold and put asterisks in front of the section I was trying to lead you to:

- m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
- study-report-aai-us-233
- study-report-aai-us-190
- study-report-aai-us-110
- m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
- study-report-mp-0104-15
- m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
- study-report-mp-0104-10
- interim-study-report-mp-0104-13
- ******m5-3-4-2-patient-pd-and-pk-pd-study-reports**
- study-report-mp-0104-16
- ******study-report-mp-0104-09**
- m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication

Michelle Ann Wells, RAC
Associate Director, Regulatory Affairs
Medicis Pharmaceutical Corporation
8125 North Hayden Road
Scottsdale AZ 85258

Main: 602 808 8800
Direct: 602 808 3851
Fax: 602 778 6051
Cell: 480 221 9968

mwells@medicis.com <mailto:mwells@medicis.com>

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Curtis, Felecia

From: Nikhar, Bindi
Sent: Friday, August 12, 2005 10:07 AM
To: See, Norman A
Cc: Luke, Markham C; Brown, Paul C; Curtis, Felecia
Subject: FW: Solodyn NDA 50-808

Norm,

I remembered later on that you had this NDA ! Please see the e mail below.

Thanks,

Bindi

-----Original Message-----

From: Nikhar, Bindi
Sent: Thursday, August 11, 2005 4:50 PM
To: Brown, Paul C
Cc: Luke, Markham C; Curtis, Felecia
Subject: Solodyn NDA 50-808

Paul,

I am not sure who the Pharmtox reviewer is for Solodyn; but I have a question for the Pharmtox team. Minocycline currently has a Pregnancy category D. For the indication of treatment of acne vulgaris, what are your thoughts on a Pregnancy Category X , since the risks in pregnancy clearly outweigh the benefits ?

Thanks,

Bindi

Curtis, Felecia

From: Nikhar, Bindi
Sent: Friday, August 12, 2005 9:16 AM
To: Luke, Markham C
Cc: Curtis, Felecia
Subject: RE: Solodyn NDA

Well, the thing is that although overall the submission is far from ideal, it would be hard to pin it down to a specific issue. Medicis knew all along that they could sneak it in....at the end of the day, it will make for a difficult review. The target date for completion could potentially be end of December if we have all the study reports in time.

Bindi

-----Original Message-----

From: Luke, Markham C
Sent: Thursday, August 11, 2005 5:07 PM
To: Nikhar, Bindi
Cc: Curtis, Felecia
Subject: RE: Solodyn NDA

OK for meeting.

So this is fileable? When are you targeting review completion (should be a date after Biostat completes)?

Thanks,
Markham

-----Original Message-----

From: Nikhar, Bindi
Sent: Thursday, August 11, 2005 4:56 PM
To: Luke, Markham C
Cc: Curtis, Felecia
Subject: Solodyn NDA

Markham,

Here is the 45 day filing list. If all is well, Felicia could incorporate it for the meeting

<< File: Solodyn 45 day filing list.DOC >>

Thanks,

Bindi



DEPARTMENT OF HEALTH & HUMAN
SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-808

Medicis
Attention: R. Todd Plott, MD
Vice President, Clinical Research & Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Dr. Plott:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: SOLODYN (minocycline hydrochloride) Modified Release
45 mg, 90 mg and 135 mg

Review Priority Classification: Standard (S)

Date of Application: June 30, 2005

Receipt Date of User Fees: July 8, 2005

Our Reference Number: NDA 50-808

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received on July 8, 2005, all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 6, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 8, 2006 .

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

NDA 50-808

Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drugs, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Felecia Curtis, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
7/29/05 02:12:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-808

Medicis
Attention: R. Todd Plott, MD
Vice President, Clinical Research & Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Dr. Plott:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Solodyn (minocycline hydrochloride) Modified Release

The Solodyn (minocycline hydrochloride) Modified Release application that was previously numbered as NDA has been re-numbered to NDA 50-808.

We refer to the guidance document issued by the Agency in May, 1998, *Guidance for Industry and Reviewers Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. This guidance document defines the administrative actions required by the Agency for reviewing and approving antibiotic drug applications that were submitted after November 21, 1997. We also refer to the *Federal Register* notice Docket Number: 99N-3088, *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs* issued January 24, 2000, which lists the active drug substances, including any derivative thereof, that are directly affected by the repeal of Section 507.

All documentation regarding this application should be directed to NDA 50-808 from this date forward.

If you have any questions, call Felecia Curtis, Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
7/29/05 02:15:56 PM

10A-27-7

MEDICIS

RECEIVED
JUL 01 2005
CDR / CDER

Form FDA 356h

June 30, 2005

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: DOCUMENT CONTROL ROOM
5901-B Ammendale Road
Beltsville, MD 20705

ORIGINAL NDA
FILING

Re: SOLODYN® (Minocycline Hydrochloride) Modified Release
45 mg, 90 mg and 135 mg

Dear Dr. Wilkin:

In accordance with the regulations set forth in 21 CFR 314.50, Medicis Pharmaceutical Corporation is submitting this New Drug Application (NDA) for SOLODYN® (Minocycline Hydrochloride) Modified Release , 45 mg, 90 mg and 135 mg.

The enclosed NDA provides for the new 45 mg, 90 mg and 135 mg strengths indicated for the treatment of the inflammatory lesions associated with moderate to severe acne vulgaris. Previous information concerning this formulation has been submitted to the Agency under investigational New Drug Application (IND) 65,398.

This submission is being submitted entirely electronically in eCTD format on CD-ROMs. Copies of each CTD section table of contents are included in the administrative folder accompanying this submission, which includes the CD sleeves and all original signed forms and certificates detailed below.

An archival copy of the administrative folder including the following forms with original signatures accompanies this electronic submission:

- Form FDA 356h, Application to Market a New Drug, Biologic, or Antibiotic Drug for Human Use
- Form FDA 3397, User Fee Cover Sheet
- Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
- Form 3452a, Patent Information Submitted with the Filing of an NDA, Amendment, or Supplement
- Debarment and Felony Conviction Certification

Medicis certifies that an identical copy of the Chemistry, Manufacturing, and Control section of this NDA is concurrently being provided to the Los Angeles District Office as a Field Copy.

The User Fee in the amount of \$672,500.00, was provided in the form of Medicis Pharmaceutical Corporation check number 182563 on June 30, 2005.

8125 North Hayden Road, Scottsdale, AZ 85258
Telephone: (602) 808-8800 Facsimile: (602) 808-0822
Web Site: <http://www.medicis.com>

Form FDA 3594a

Debarment
Certification

Field Copy
Certification

Form FDA 3397
User Fee Cover Sheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Medicis Pharmaceutical Corp

DATE OF SUBMISSION

2/16/06

TELEPHONE NO. (Include Area Code)

602-808-8800

FACSIMILE (FAX) Number (Include Area Code)

602-778-6051

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

8125 North Hayden Road Scottsdale AZ 85258

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 50-808

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Minocycline Hydrochloride

PROPRIETARY NAME (trade name) IF ANY

SOLODYN™ Modified Release

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

[4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monoHCl

CODE NAME (if any)

DOSAGE FORM:

Modified Release Caplets

STRENGTHS:

45, 90 and 135 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

SOLODYN (modified-release minocycline) caplets are indicated for the treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

- 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)

- ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

- CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Response to February 9, 2006 FDA request for Clinical Information

PROPOSED MARKETING STATUS (check one)

- PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

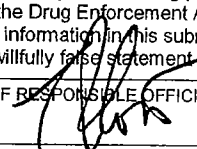
- PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 65,398

This application contains the following items: <i>(Check all that apply)</i>		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling <i>(check one)</i>	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input checked="" type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input type="checkbox"/>	20. OTHER <i>(Specify)</i>	
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	R. Todd Plott, MD, VP Clinical Research & Reg. Affairs	2/16/06
ADDRESS <i>(Street, City, State, and ZIP Code)</i>		Telephone Number
8125 N. Hayden Road, Scottsdale AZ 85258		(602) 808-8800
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NDA REGULATORY FILING REVIEW

NDA # **50-808**

Supplement # **N/A**

Efficacy Supplement Type **SE-**

Trade Name: **Solodyn**

Established Name: **minocycline hydrochloride**

Strengths: **Modified Release (— 45 mg, 90 mg & 135 mg**

Applicant: **Medicis**

Agent for Applicant: **N/A**

Date of Application: **June 30, 2005**

Date of Receipt: **July 1, 2005**

Date clock started after UN: **July 8, 2005**

Date of Filing Meeting: **August 15, 2005**

Filing Date: **September 6, 2005**

74 Day Letter: **September 20, 2005**

Clin/Stat Mtg: **October 12, 2005**

Mid Cycle Review Mtg: **November 30, 2005**

Date of Labeling Meeting: **TBD**

Target Date (optional): **May 8, 2006**

User Fee Goal Date: **May 8, 2006**

Indication(s) requested: **Treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.**

Type of Original NDA: (b)(1) (b)(2)
OR

Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b).*

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO

If an electronic NDA, all forms and certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Additional comments: **Links not in correct sections. Clinical microbiology section located in the Reports of Human Pharmacodynamics (PD) Studies.**

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO

If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates. **Request made on 8/12/05.**
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: **65,398**
- End-of-Phase 2 Meeting(s) Date(s) September 17,, 2003 NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) Date(s) March 28, 2005 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Will send after filing. YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
 Will send after filing.
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
 Will send after filing.
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A X YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? N/A X YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A X YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? XN/A YES NO

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
9/29/2005 11:57:54 AM
CSO

Mary Jean Kozma Fornaro
10/3/2005 11:15:49 AM
CSO

NDA REGULATORY FILING REVIEW

NDA # **50-808**

Supplement # **N/A**

Efficacy Supplement Type **SE-**

Trade Name: **Solodyn**

Established Name: **minocycline hydrochloride**

Strengths: **Modified Release** — **45 mg, 90 mg & 135 mg**

Applicant: **Medicis**

Agent for Applicant: **N/A**

Date of Application: **June 30, 2005**

Date of Receipt: **July 1, 2005**

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74 Day Letter: **September 20, 2005**

Clin/Stat Mtg: **October 12, 2005**

Mid Cycle Review Mtg: **November 30, 2005**

Date of Labeling Meeting: **TBD**

Target Date (optional):

May 8, 2006

User Fee Goal Date:

May 8, 2006

Indication(s) requested: **Treatment of the inflammatory lesions associated with moderate to severe acne vulgaris.**

Type of Original NDA:

(b)(1)

(b)(2)

OR

Type of Supplement:

(b)(1)

(b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application

OR

NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted:

YES NO

User Fee Status:

Paid

Exempt (orphan, government)

Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b).*

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments: **Links not in correct sections. Clinical microbiology section located in the Reports of Human Pharmacodynamics (PD) Studies.**

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO

- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates. **Request made on 8/12/05.**

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **65,398**

- End-of-Phase 2 Meeting(s)? Date(s) September 17,, 2003 NO
 If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 28, 2005 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
 If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Will send after filing. YES NO

- Risk Management Plan consulted to ODS/IO? N/A YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
 Will send after filing.

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
 Will send after filing.

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? N/A YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? ~~X~~N/A YES NO

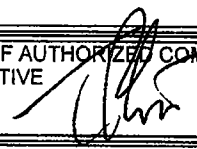
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/s/

Felicia Curtis
9/29/2005 11:57:54 AM
CSO

Mary Jean Kozma Fornaro
10/3/2005 11:15:49 AM
CSO

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm		
1. APPLICANT'S NAME AND ADDRESS MEDICIS PHARMACEUTICAL CORP R. Todd Platt MD 8125 NORTH HAYDEN ROAD SCOTTSDALE AZ 85258 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-783	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
2. TELEPHONE NUMBER 602-808-3851	3. PRODUCT NAME SOLODYNE(R) (Minocycline Hydrochloride Modified Release	6. USER FEE I.D. NUMBER PD3006110
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Food and Drug Administration CDER, HFD-94 CBER, HFM-99 12420 Parklawn Drive, Room 3046 1401 Rockville Pike Rockville, MD 20852 Rockville, MD 20852-1448		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE VP	DATE 6/7/05
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$672,000.00		
Form FDA 3397 (12/03)		

(Close) (Print Cover sheet)