

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-808**

**CHEMISTRY REVIEW(S)**



**NDA 50-808**

**Solodyn  
(MINOCYCLINE HCl, USP) EXTENDED -RELEASE  
TABLETS**

**Medicis**

**Shrikant N. Pagay  
Office of Pharmaceutical Sciences CMC Review**



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# Chemistry Review Data Sheet

1. NDA 50-808
2. REVIEW #: 1
3. REVIEW DATE: 24<sup>th</sup> April 2006
4. REVIEWER: Shrikant N. Pagay
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original	6/30/05
Amendment- BC-Response to Comments	2/17/06
Correspondence- withdrawal of Boston Anal.	2/28/06
Amendment -BL - CMC label changes	3/3/06
Amendment - BC- Response to Comments	3/14/06
Amendment - BL - CMC Label chnages	3/22/06
Amendment - BL - CMC Label chnages	3/30/06
Amendment - BL - CMC Shelf life	4/19/06
Telecon / Dissolution Spec.	4/21/06

7. NAME & ADDRESS OF APPLICANT:

Name: Medicis

Address: 8125 North Hayden, Scottsdale, AZ 85258

Representative:

Dr. Todd Plott

Telephone:

(602)- 778- 3851



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Solodyn
- b) Non-Proprietary Name (USAN): Minocycline hydrochloride
- c) Code Name/# (ONDC only): NA
- d) Chem. Type/Submission Priority (ONDC only): NA
  - Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anti-infective

11. DOSAGE FORM: Extended Release Tablet

12. STRENGTH/POTENCY: 45mg, 90 mg and 135 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name: [4S-4a, 4aa, 5aa, 12aa]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride.

CAS Registry Number: 13614-98-7

Molecular Formula:  $C_{22}H_{27}N_3O_7 \cdot HCl$

Molecular Weight: 493.95

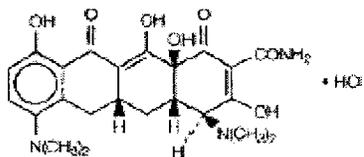
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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	4/11/2003	Zuk
	III			3	Adequate	11/9/2004	Klein
	III			3	Adequate	4/29/2004	Pope
	III			3	Adequate	7/2/1999	Cumming
	III			3	Adequate	1/12/2004	Madurawe
	III			3	Adequate	1/12/2004	Cooper
	III			3	Adequate	12/7/2005	Frankewich
	III			3	Adequate	1/12/2005	Madurawe
	III			3	Adequate	7/26/2004	Hsieh
	III			3	Adequate	10/23/2003	Tso
	III			3	Adequate	1/21/2005	Madurawe
	III			3	Adequate	12/7/2005	Frankewich
	III			3	Adequate	1/22/2004	Matecka
	III			3	Adequate	7/29/2004	Hsieh
	III			3	Adequate	9/25/2002	Kang
	III			3	Adequate	4/20/2000	SeEVERS

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,398	

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	8/22/2005	
Pharm/Tox	NA		
Biopharm	NA		
LNC/DMETS	Acceptable	6/30/05	
Methods Validation	NA		
DMETS	Acceptable	6/30/05	
EA	NA		
Microbiology	NA		

### 19. COMMENTS:

Please note that all italicized portion of Chemistry Assessment Section are reviewer's comments. The remaining information (data, figures and some responses to deficiencies) are directly incorporated from the submission. Information provided in the Chemistry Review Data Sheet and the Executive Summary Sections are reviewer's comments.

Regulatory specifications, i.e., specifications agreed upon CMC review, EER, expiration date of the drug substance and shelf life of the drug product, stability study commitments are listed in the appropriate review sections.

The drug product is labeled as a tablet (capsule shaped tablet) in the submission. Review includes both tablet and tablet terminology for the same dosage form. The approved label will only include tablet terminology.

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# The Chemistry Review for NDA 50-808

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA can be approved from CMC perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable:

No Phase IV commitment from CMC perspective.

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

##### Drug Substance

Minocycline hydrochloride is a tetracycline class of antibiotics

yellow, crystalline material

It is a broad spectrum antibiotic.

Tetracycline class of antibiotic exerts anti-infective action as bacteriostatic agents. The mechanism of action is attributed to inhibition of protein synthesis in microorganisms. Chemically, all tetracycline share a partially reduced naphthacene ring system designated as ABCD as shown in Figure 1.

Figure 1- General Chemical Structure for Tetracycline

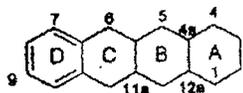
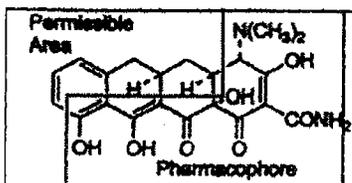


Figure 2 below shows that the lower periphery of the BCD ring system and all of A ring has the same substituent groups for all microbiologically active tetracycline such as minocycline, chlortetracycline, tigecycline and other approved tetracycline.



Any change in these groups will reduce the bioactivity; therefore this entire group in the above figure is designated as pharmacophore group. Chemical changes are made in the permissible area to alter the drug absorption, duration of action, physical and chemical properties resulting in several approved new chemical entities of tetracycline class including minocycline. Several NDAs of



Executive Summary Section

different dosage forms of minocycline have been approved since 1971. However, minocycline extended release tablet has not been approved. The drug substance for the NDA is obtained under DMF [redacted]. The manufacturer holds DMF for several other antibiotics indicating that [redacted] is an established manufacturer of fermentation antibiotics drug substances. Minocycline unlike other antibiotics contains 2 amino groups which are responsible for high aqueous solubility under neutral pH. Also, the octanol/water partition coefficient is at its maximum at pH 6.6 suggesting good drug absorption from a tablet dosage form.

Drug Product

The dosing regimen for anti-infective agents such as minocycline is a critical issue for optimum therapy. Since antibiotics are given in large doses, developing an extended release formulation is difficult which has been achieved in this submission. This formulation is designed to achieve a desired objective, i.e., to release the drug slowly. The manufacturing process for this controlled release tablet is well established.

[redacted] critical for matrix tablets when the tablet hardness controls dissolution rate. The more critical control, such as the dissolution specifications of the finished drug product were agreed upon after discussion with the Agency and on the basis of the available stability data and CDER Dissolution Guidance. Also, USP <711> acceptance criteria stage 2 and stage 3 provision for dissolution were taken into consideration in setting the dissolution specifications.

The drug product is an extended release capsule shaped tablet. The three tablets strengths 45 mg, 90 mg, and 135 mg have the same physical dimensions but each of the 3 tablet strengths is film coated with a different color coating composition and debossed for easy identification. The inactive components include lactose monohydrate, hypromellose, [redacted], silicon dioxide, [redacted], magnesium stearate, Opadry [redacted], carnauba wax, [redacted]

The 45 mg tablets are gray, 90 mg tablets are yellow and 135 mg tablets are pink. The tablets are packaged in [redacted]. Based on the formulation design and the in-vitro dissolution profile, the dosage form meets USP criterion for extended release tablet. The pharmacokinetics data supports extended release based on a Tmax of up to 4 hours compared to immediate-release reference drug product from the same applicant with Tmax at 2.25-3 hours.

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

Solodyn tablets (MINOCYCLINE HCl, USP) EXTENDED-RELEASE TABLETS are indicated for the treatment of the inflammatory lesions associated with moderate to severe acne vulgaris. Solodyn is supplied in tablet strengths - 45 mg, 90 mg and 135 mg. of minocycline. The recommended dosing is 1 mg/Kg body weight based on 3 clinical studies. Each study was a 12-week prospective, multi-center, randomized, double blind placebo-controlled study. The dosing is once a day. Minocycline extended release tablets can be administered with or without food.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug substance is well characterized and had been approved in previous applications for other dosage forms. The proposed drug product is an extended release dosage form available in 3 strengths (45mg, 90 mg and 135 mg tablets); the critical product attributes (potency, impurities and dissolution) are well controlled based on sufficient stability data. Overall, all 3 strengths of the drug product are well controlled. The Compliance inspection for all the manufacturing and control facilities was satisfactory. Sufficient stability information per ICH guidance was provided to assess the shelf life of the drug product. The drug product labeling complies with all regulatory requirements.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Shrikant N. Pagay  
Chemistry Branch Chief Name /Date: Moo Johng Rhee  
Project Manager Name/Date:

**C. CC Block**

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       Draft Labeling

       Deliberative Process

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/s/

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Chief, Branch III