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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      c. Flow Chart ............................................................................................................... Error! Bookmark not defined.

NDA 50-808
Solodyn
(Minocycline HCl, USP)Extended-Release Tablets
d. Detailed Description

4. Process Controls
   a. Reaction Completion / Other In-Process Tests
   b. Intermediate Spec's / Tests

5. Reference Standard
   a. Preparation
   b. Specifications

6. Regulatory Specifications / Analytical Methods
   a. Drug Substance Specifications & Tests
   b. Purity Profile
   c. Microbiology

7. Container/Closure System For Drug Substance Storage

8. Drug Substance Stability

II. DRUG PRODUCT

1. Components/Composition

2. Specifications & Methods For Drug Product Ingredients
   a. Active Ingredient(s)
   b. Inactive Ingredients

3. Manufacturer

4. Methods Of Manufacturing And Packaging
   a. Production Operations
   b. In-Process Controls & Tests
   c. Reprocessing Operations

5. Regulatory Specifications And Methods For Drug Product
   a. Sampling Procedures
   b. Regulatory Specifications And Methods

6. Container/Closure System

7. Microbiology

8. Drug Product Stability

III. INVESTIGATIONAL FORMULATIONS

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NDA 50-808
Solodyn
(Minocycline HCl, USP)Extended-Release Tablets
Chemistry Review Data Sheet

1. NDA 50-808

2. REVIEW #: 1

3. REVIEW DATE: 24th April 2006

4. REVIEWER: Shrikant N. Pagay

5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: Medicis

Address: 8125 North Hayden, Scottsdale, AZ 85258

Representative: Dr. Todd Plott

Telephone: (602)- 778- 3851
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: _X_Rx _ _OTC

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

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

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

   CAS Registry Number: 13614-98-7

   Molecular Formula: C_{25}H_{27}N_{3}O_{7} . HCl

   Molecular Weight: 493.95

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

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
B. Other Documents: NA

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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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On Original
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 Approvable:

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. 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 naphthalene ring system designated as ABCD as shown in Figure 1.

Figure 1 - General Chemical Structure for Tetracycline

![Chemical Structure for Tetracycline](image)

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.

![Pharmacophore](image)

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
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. The manufacturer holds DMF for several other antibiotics indicating that it 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.

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, silicon dioxide, magnesium stearate, Opadry, and carnauba wax.

The 45 mg tablets are gray, 90 mg tablets are yellow and 135 mg tablets are pink. The tablets are packaged in 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 John Rhee
Project Manager Name/Date:

C. CC Block

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

/s/

Shrikant Pagay
4/24/2006 03:51:32 PM
CHEMIST

Moo-Jhong Rhee
4/24/2006 04:42:21 PM
CHEMIST
Chief, Branch III