

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** NDA 50-781

---

**CHEMISTRY REVIEW(S)**

**DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS**  
Review of Chemistry, Manufacturing, and Controls

**NDA #: 50-781      REVIEW #: 1      REVIEW DATE:      05-FEB-2001**

<b><u>SUBMISSION</u></b> <b><u>TYPE</u></b>	<b><u>DOCUMENT</u></b> <b><u>DATE</u></b>	<b><u>CDER</u></b> <b><u>DATE</u></b>	<b><u>ASSIGNED</u></b> <b><u>DATE</u></b>
Original	16-FEB-2000	17-FEB-2000	22-FEB-2000
Amendment/BC	17-FEB-2000	18-FEB-2000	07-MAR-2000
Amendment/BC	11-APR-2000	12-APR-2000	18-APR-2000
Amendment/BC	19-APR-2000	18-JAN-2001	19-JAN-2001
Amendment/BC	05-JUN-2000	06-JUN-2000	09-JUN-2000
Amendment/BC	19-JUN-2000	21-JUN-2000	28-JUN-2000
Amendment/BC	29-JUN-2000	03-JUL-2000	07-JUL-2000
Amendment/BL	16-AUG-2000	18-AUG-2000	25-AUG-2000
Amendment/BC	11-SEP-2000	13-SEP-2000	27-SEP-2000
Amendment/BC	09-OCT-2000	11-OCT-2000	16-OCT-2000
Amendment/BC	03-NOV-2000	06-NOV-2000	08-NOV-2000
Amendment/BC	06-NOV-2000	07-NOV-2000	15-JUN-2000
Amendment/BC	09-NOV-2000	13-NOV-2000	15-NOV-2000
Amendment/BL	01-DEC-2000	04-DEC-2000	06-DEC-2000
Amendment/BL	03-JAN-2001	05-JAN-2001	08-JAN-2001
Amendment/XR	09-JAN-2001	10-JAN-2001	18-JAN-2001
Amendment/BC	10-JAN-2001	11-JAN-2001	18-JAN-2001
Amendment/BC	25-JAN-2001	26-JAN-2001	02-FEB-2001
Amendment/BC	30-JAN-2001	01-FEB-2001	07-FEB-2001

**NAME & ADDRESS OF APPLICANT:**

OraPharma, Inc.  
732 Louis Drive  
Warminster, PA 18974

**CONTACT PERSON:**

Markus F. Herzig  
Executive Director of Regulatory Affairs  
(215) 956-2200 Tel  
(215) 443-9531 Fax

**DRUG PRODUCT NAME**

**Proprietary:**

Arestin™

**Nonproprietary/USAN:**

Minocycline Hydrochloride

**Code Name/#:**

None

**Chem.Type/Ther.Class:**

3S

**PHARMACOL. CATEGORY/INDICATION:** Anti-microbial for local prophylaxis of periodontal infection

**DOSAGE FORM:** Controlled release polymer containing 1 mg minocycline

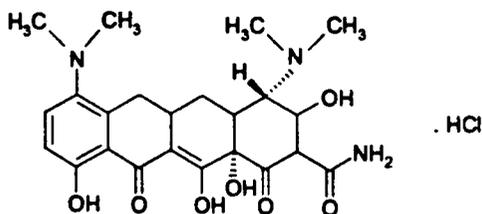
**STRENGTHS:** 1 mg

**ROUTE OF ADMINISTRATION:** Subgingival

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

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 Number: 13614-98-7)

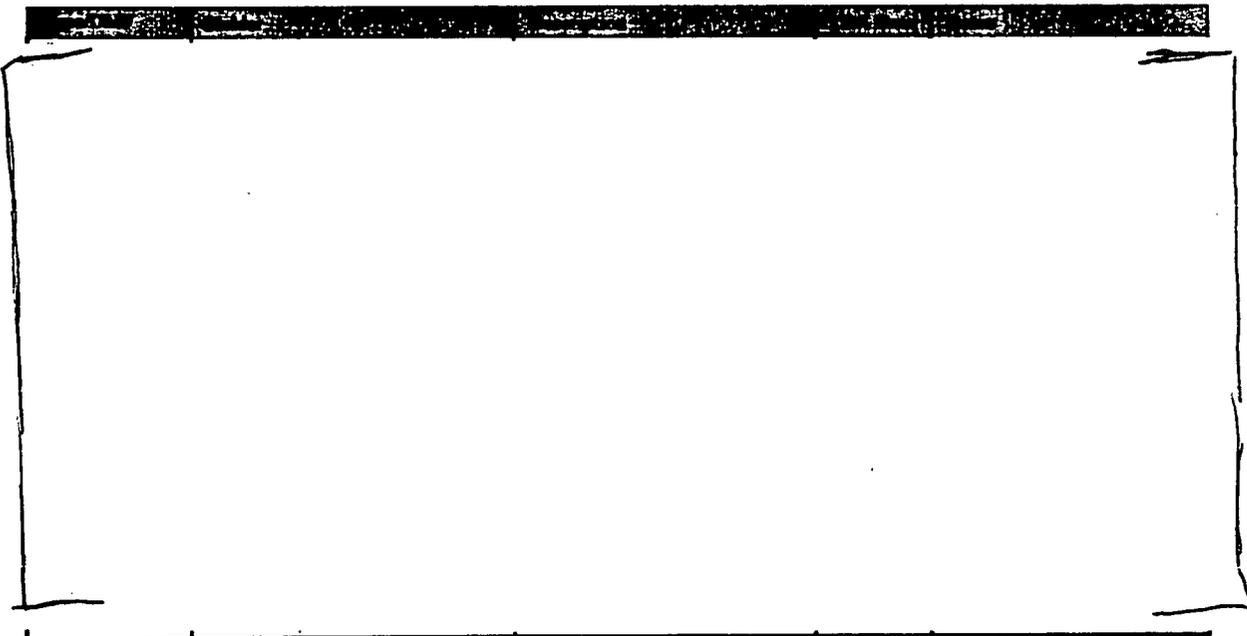
Molecular Formula:  $C_{23}H_{27}N_3O_7 \cdot HCl$ , Molecular Weight: 493.95



Minocycline Hydrochloride

**SUPPORTING DOCUMENTS:**

IND \_\_\_\_\_, Microbiology Review #1 dated August 7, 2000 ( NDA amendment dated June 5, 2000) and DMFs listed below:



**REMARKS/COMMENTS:**

1. Arestin™, Microspheres, 1 mg consists of Minocycline Hydrochloride encapsulated in a bioresorbable polymer, poly(glycolide-co-dl-lactide). The formulation of to-be-marketed drug product is the same as that used in clinical studies.
2. Filling/packaging operation was changed (amendment dated 11/3/00) from that employed for the clinical batches. (See Drug Product: Section 5, for details). Limited analytical data suggests no significant differences (amendment dated 1/25/01) in quality attributes (e.g. particle size distribution) of the drug product when packaged using the new filling machine.

Minocycline release rates were found to be lower for the drug product packaged using the new filling machine. This was discussed in an 'all discipline' team meeting held on 1/16/01. The team did not express any concerns regarding the safety and efficacy that might be attributed to lower release rates.

3. Release rate specifications include the acceptance limits of 'Not Less Than' (NLT) instead of 'lower and upper' or 'two-sided' acceptance limits. An amendment to the Biopharm Review requesting a Phase 4 commitment to revise release rate specifications based on the historical data was recommended at the team meeting (1/16/01).
4. Revised bulk drug product specifications with particle size specifications were submitted in amendment dated 1/25/01. Method validation data for Particle Size Analysis will be submitted in near future. Since particle size specification is not a Regulatory Specification for the finished drug product in reviewer's opinion the absence of validation data at this time is not considered an approvability issue.
5. Long term (upto 18 months) stability data for primary stability batches supports the proposed expiration date of 24 months when stored at 25°C (see Stability Section for details).

The examinations of individual release rate stability data (amendment dated 11/6/00) show high degree of variability but met the current specifications. For drug release rate, the overall pattern of change with time shows an increase in amount released at 4 hour and decrease in release at 24, 48, and 72 hours. Actual results from primary stability studies (through 18 months) and the supporting studies (through 24 months) support the proposed expiration date.

6. The cGMP status of all facilities that will perform manufacturing, packaging and controls for the drug substance, critical excipient, and drug product is ACCEPTABLE per the OC recommendation dated January 31, 2001.

**CONCLUSIONS & RECOMMENDATIONS:**

Recommend approval from the CMC perspective.

---

**Mamta Gautam-Basak, Ph.D.**  
Review Chemist

cc:

Org. NDA 50-781/000

HFD-540/Division File

HFD-540/PM/Bhatt

HFD-540/MO/Gilkes

HFD-540/PhmTox/See

HFD-540/Chm/Gautambasak

HFD-540/Chm/TL/DeCamp

/s/

-----  
Mamta Gautam-Basak  
2/8/01 01:52:45 PM  
CHEMIST

goal date 2/16/01, page lay out for Tables fixed, Thanks,

Wilson H. DeCamp  
2/8/01 01:56:51 PM  
CHEMIST  
concur with review

---

---

WITHHOLD 27 PAGE (S)

---

WITHHOLD 4 PAGE (S)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** NDA 50-781

---

**ENVIRONMENTAL ASSESSMENT and/or FONSI**

---

WITHHOLD 1 PAGE (S)