CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-744

CHEMISTRY REVIEW(S)

NDA 21-744

Proquin™ XR

(ciprofloxacin hydrochloride) Extended-Release Tablets, 500 mg

Depomed, Inc.

Balajee Shanmugam
HFD-590
Division of Special Pathogen and Immunologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-744

2. REVIEW #: 1

3. REVIEW DATE: 18-MAY-2005

4. REVIEWER: Balajee Shanmugam, Ph.D.

5. PREVIOUS DOCUMENTS: NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	18-Jul-2004
Amendment (BC)	23-Nov-2004
Amendment (BZ)	22-Dec-2004
Response to IR (email)	02-Feb-2005
Amendment (BC)	09-Feb-2005
Response to IR (email)	11-Apr-2005
Response to IR (email)	12-Apr-2005
Response to IR (email)	18-Apr-2005
Response to IR (email)	22-Apr-2005
Response to IR (email)	05-May-2005
Response to IR (email)	09-May-2005
Response to IR (email)	10-May-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Depomed, Inc.

Address: 1360 O'Brien Drive, Menlo Park, CA 94025

Representative: Bret Berner, PhD

Telephone: 650-462-5900

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Proquin™ XR
b) Non-Proprietary Name (USAN): ciprofloxacin
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibacterial

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

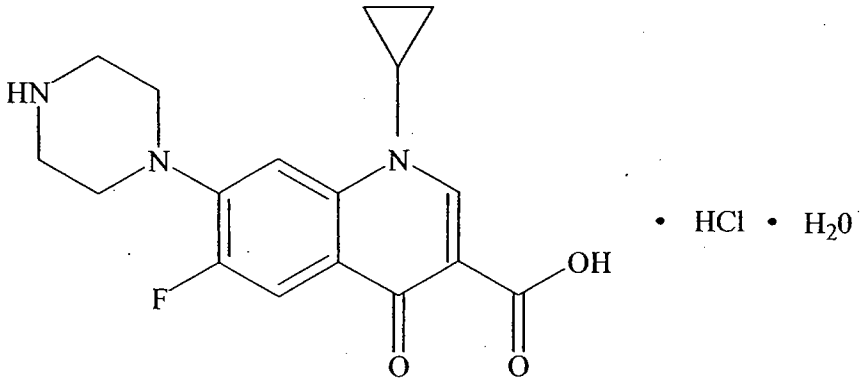
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate.

Molecular formula: $C_{17}H_{18}FN_3O_3$. HCl . H_2O
Molecular weight: 385.82
Molecular weight (base): 331.4
CAS: 86393-32-0



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	26-May-2004	N/A
	III			3	Adequate	27-May-2003	N/A
	IV			3 and 4	Adequate	18-Oct-2004	N/A
	III			3 and 4	Adequate	22-Jul-2004	N/A
	III			4	Adequate	20-Dec-2004	N/A
	III			3 and 4	Adequate	01-Sep-1999	N/A
	III			4	Adequate	10-Jan-2005	N/A

[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:

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a	n/a	n/a
EES	Acceptable	02-MAY-05	J. D Ambrogio, HFD-322
Pharm/Tox	n/a		
Biopharm	n/a		
LNC	n/a		
Methods Validation	Not requested		
DMETS	Trademark acceptable. Use of XR etc. not recommended.	08-AUG-04	C. Hoppes, HFD-420
EA	Categorical exclusion	31-MAR-2005	B. Shanmugam
Microbiology	n/a	n/a	n/a

The Chemistry Review for NDA 21-744

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the chemistry, manufacturing and controls perspective.

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

While no recommendations for Phase 4 CMC commitments are made, the firm should, as committed in the submission, continue to monitor the stability of the drug product.

II. Summary of Chemistry Assessments

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

The drug product is formulated as an extended-release tablet containing 500 mg of ciprofloxacin. The tablets are blue, film coated, 0.3937" X 0.37086", oval shaped and weigh 803.33 mg. The manufacture of the drug product involves [redacted] The tablet contains 500 mg of ciprofloxacin, as ciprofloxacin HCl monohydrate (ciprofloxacin HCl, USP). Excipients used in the manufacture are compendial-grade with the exception of Opadry Blue. [redacted] The swelling of the tablet promotes its retention in the stomach during the fed mode and the [redacted] over time releasing the drug from the tablet. Approximately 90% of the 500 mg dose that is released is claimed to be delivered to the upper gastrointestinal (GI) tract, which is where ciprofloxacin is best absorbed. The drug product exhibits good stability when stored at 25°C/60% RH.

The drug substance ciprofloxacin is a synthetic broad-spectrum fluoroquinolone antibiotic. Ciprofloxacin hydrochloride is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid hydrochloride. The drug substance occurs as a faintly yellowish to light yellow crystals. It is sparingly soluble in water and slightly soluble in acetic acid and methanol. The drug substance, ciprofloxacin is used in many other approved products and available in the trade market in different dosage

forms. These include CIPRO® tablets (immediate and extended-release formulations), and CIPRO® I.V. For this NDA, the firm has provided a LOA to reference DMF , for drug substance CMC. The DMF was previously reviewed and found to be adequate.

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

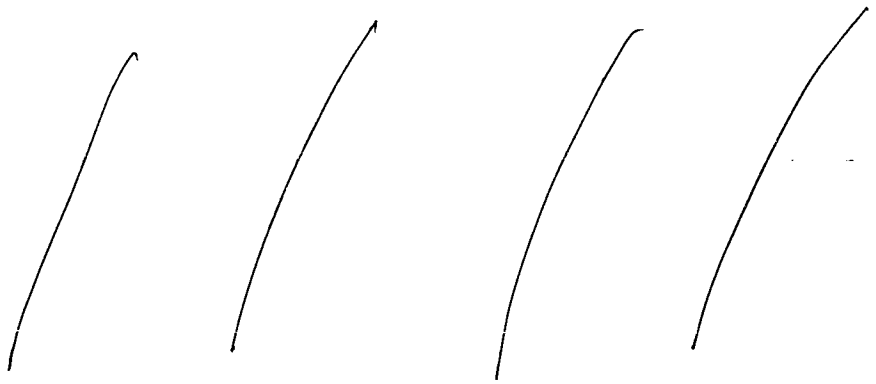
Proquin™ XR is indicated for the treatment of uncomplicated urinary tract infections (acute cystitis). The intended dosing regimen is a 500-mg once daily for oral administration following a — meal.

The stability studies support an expiration dating period of 24 months for product stored at 25°C/60% RH.

C. Basis for Approvability or Not-Approval Recommendation

The original submission and the subsequent amendments submitted by the firm have provided adequate information describing the CMC for Proquin™ (ciprofloxacin HCl) extended-release tablets.

The DMF for the drug substance was reviewed previously and found to be adequate. The inactive ingredients used in the drug product are compendial except for Opadry Blue for which the company has provided adequate information in the NDA submission. In addition, the firm also provided reference to a DMF for Opadry Blue. The manufacturing process for the drug product has been adequately described. The company proposed



All issues regarding the drug product specifications have been adequately negotiated with the applicant. The company has established key process parameters in the manufacture of the drug product. The applicant will continue to monitor the stability of the drug substance and drug product. The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

In accordance to 21 CFR 314.50, the application provides adequate information on manufacturing and packaging procedures, in-process controls, methods, and specifications.

III. Administrative

A. Reviewer's Signature

{see Electronic Signature Page}

B. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

57 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Balajee Shanmugam
5/18/05 02:27:36 PM
CHEMIST
CMCReview/NDA21-744

Mark Seggel
5/18/05 02:35:14 PM
CHEMIST

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_____ Deliberative Process