

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-473

CHEMISTRY REVIEW(S)

NDA 21-473

Cipro XR (ciprofloxacin extended-release tablets)

**BAYER CORPORATION
PHARMACEUTICAL DIVISION**

**Dorota Matecka
Division of Special Pathogen and Immunologic Drug
Products, HFD-590**

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-473
2. REVIEW #: 1
3. REVIEW DATE: 9-Dec-2002
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	4-Mar-2002
Amendment (NC)	18-Jul-2002
Amendment (BC)	7-Aug-2002
Amendment (BC)	20-Sep-2002
IR letter (email)	5-Nov-2002
Amendment (BC)	21-Nov-2002
Amendment (BC)	6-Dec-2002

6. SUBMISSION(S) BEING REVIEWED:

<u>Previous Documents</u>	<u>Document Date</u>
Original	4-Mar-2002
Amendment (NC)	18-Jul-2002
Amendment (BC)	7-Aug-2002
Amendment (BC)	20-Sep-2002
Amendment (BC)	21-Nov-2002
Amendment (BC)	6-Dec-2002

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Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer Corporation Pharmaceutical Division
Address:	400 Morgan Lane, West Haven, CT 06516
Representative:	Andrew Verderame, Associate Director, Regulatory Affairs
Telephone:	(203) 812-5172

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: CIPRO XR
- b) Non-Proprietary Name (USAN): ciprofloxacin extended-release tablets
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: antibacterial

11. DOSAGE FORM: extended-release tablets

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

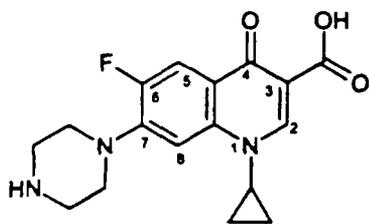
Not a SPOTS product

CHEMISTRY REVIEW

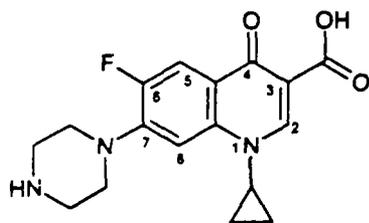
Chemistry Review Data Sheet

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

Ciprofloxacin — (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid); 331.4 (anhydrous basis) — 3.5 hydrate); $C_{17}H_{18}N_3FO_3$ (anhydrous basis); $C_{17}H_{18}N_3FO_3 \times 3.5 H_2O$ (3.5 hydrate)



Ciprofloxacin hydrochloride (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride monohydrate); 385.8; $C_{17}H_{18}N_3FO_3 \times HCl \times H_2O$



• HCl
• H₂O

17. RELATED/SUPPORTING DOCUMENTS:

APPEARS THIS WAY
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CHEMISTRY REVIEW

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	20-Nov-2002	N/A
	II			1	Adequate	9-Dec-2002	N/A
	III			4	N/A	N/A	N/A
	III			3* and 4	Adequate	12/13/99	N/A
	III			3* and 4	Adequate	6/30/99	Acceptable for LR-734-45
	III			3* and 4	Adequate	12/19/00	N/A
	III			3* and 4	Adequate	7/13/99 and 7/26/00	N/A
	III			3	Adequate	4/25/02	N/A
	III			3* and 4		12/03/97	N/A
	III			3	Adequate	9/18/00	Acceptable for 75M seal
	III			3	Adequate	6/06/02	Acceptable for PH010B2
	III			3	Adequate	1. 8/23/02 2. 6/13/02	N/A

* Reviewed previously, as indicated by the review date received from the Comis database. It was not verified if any revisions were made since the last review, however for this NDA, sufficient information regarding the container/closure systems for the drug product was provided in the application as described in the review below

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)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	3-Dec-2002	Janine D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	Acceptable	10-Oct-2002	Dan Boring
Methods Validation	Not submitted yet	N/A	N/A
DMETS	Acceptable	31-Aug-2002	Carol Holquist
EA	Categorical exclusion	N/A	N/A
Microbiology	N/A	N/A	N/A

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The Chemistry Review for NDA 21-473

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

The drug substance, ciprofloxacin, is a synthetic broad-spectrum antimicrobial agent available on the market in several other formulations (e.g. CIPRO Tablets and CIPRO I.V.).

CIPRO XR tablets contains two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and Ciprofloxacin (hydrated form of ciprofloxacin base).

For the majority of chemistry, manufacturing and controls information regarding ciprofloxacin hydrochloride the reference is made to [redacted]. The retest period for the ciprofloxacin hydrochloride drug substance is 24 months.

For the majority of chemistry, manufacturing and controls information regarding Ciprofloxacin (hydrated form of ciprofloxacin base) reference is made to [redacted]. Ciprofloxacin [redacted] is a hydrated form of ciprofloxacin base, which consists mainly of the 3.5 hydrate (theoretically [redacted] of water per molecule of ciprofloxacin). The information regarding the [redacted] of Ciprofloxacin [redacted] is provided in both DMF and NDA. Ciprofloxacin [redacted] for the use in CIPRO XR tablets is [redacted]. The [redacted] step description and the specification for the [redacted] Ciprofloxacin [redacted] are provided in the NDA. The retest period for the Ciprofloxacin [redacted] drug substance is 12 months.

CIPRO XR tablets have been developed, based on conventional [redacted] principle (with [redacted] as the retardation agent), as [redacted] two-layer tablets with the following characteristics:

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Executive Summary Section

- 2-layer tablet with IR (immediate release) layer for fast dissolution of the drug and absorption in the upper GI tract, and CR (controlled release) layer for achievement of sufficient plasma levels over a prolonged period of time;
- 2 types of ciprofloxacin (ciprofloxacin hydrochloride and ciprofloxacin base, both in each layer in different proportion), which contribute to minimize pH dependent effects on dissolution

Each CIPRO XR 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (212.6 mg, calculated on the dried basis)

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

CIPRO XR tablets are available as 500-mg coated tablets for a once-a-day treatment of uncomplicated urinary tract infections. The tablets are packaged in three packaging configurations, HDPE 150 cc bottles (of 100 tablets), HDPE 120 cc bottles (of 50 tablets), and PVC/PVDC clear blisters.

The proposed expiration dating of 24 months as proposed by the applicant for CIPRO XR tablets is acceptable. The storage conditions statement recommends the storage at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of CIPRO XR (ciprofloxacin extended-release tablets). During the review a number of issues, including the following were resolved.

The specification for one of the drug substances (ciprofloxacin base), specifically the acceptance criteria for the loss on drying particle size distribution were revised.

The specification for the drug product was also revised to include test and acceptance criteria for water content. Acceptance criteria for the impurities in the drug product were revised.

The trade name was found acceptable by OPDRA and by the Division HFD-590. The established name was further consulted with the Labeling and Nomenclature Committee and it was recommended as following:

CIPRO-XR (ciprofloxacin* extended-release tablets)

* as ciprofloxacin † and ciprofloxacin hydrochloride

† does not comply with the loss on drying test and residue on ignition test of the USP monograph.

Several changes in the DESCRIPTION section of the labeling were recommended to the applicant.

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Executive Summary Section

III. Administrative

A. Reviewer's Signature

DFS (electronic)

B. Endorsement Block

Chemist: Dorota Matecka/11/25/02

Chemistry TL: Norman Schmuff

PM: Jouhayna Saliba

C. CC Block

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**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

35 pages

CHEMISTRY REVIEW

Chemistry Assessment Section

09-DEC-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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Profile : CEM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-APR-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CPN : 1216486 FEI : 1216486
BAYER CORP
400 MORGAN LANE
WEST HEAVEN, CT 065164175

DMP No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-APR-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CPN : 9614785 FEI : 3002804461
BAYER SPA
120024
GARRAGATE, MILAN, IT 1-20024

DMP No: 10353 AADA:

Responsibilities: DRUG SUBSTANCE MICROBIKER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CRU OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-DEC-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

/s/

Dorota Matecka
12/10/02 10:21:26 AM
CHEMIST

Norman Schmuff
12/10/02 02:24:31 PM
CHEMIST

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ON ORIGINAL**