

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-554**

**Chemistry Review(s)**

**NDA 21-554**

**CIPRO XR (ciprofloxacin extended-release tablets),  
1000-mg**

**BAYER PHARMACEUTICALS CORPORATION**

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

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# Chemistry Review Data Sheet

1. NDA 21-554
2. REVIEW #: 1
3. REVIEW DATE: 27-Aug-2003
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	29-Oct-2002
Amendment (BC)	20-Jan-2003
Amendment (BC)	6-Jun-2003
Amendment (BC)	5-Aug-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Previous Documents</u>	<u>Document Date</u>
Original	29-Oct-2002
Amendment (BC)	20-Jan-2003
Amendment (BC)	6-Jun-2003
Amendment (BC)	5-Aug-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Bayer Pharmaceuticals Corporation
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: 1000 mg

## 13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

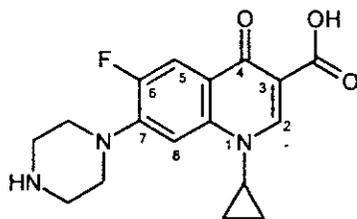
SPOTS product - Form Completed

Not a SPOTS product

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

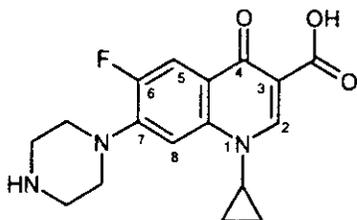
Ciprofloxacin hydrochloride (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride (mixture of monohydrate and sesquihydrate);  $C_{17}H_{18}N_3FO_3 \cdot x HCl$  ( $H_2O$  and  $1.5 H_2O$ ); 367.8 (anhydrate); 385.8 (monohydrate)

## Chemistry Review Data Sheet



- HCl
- H<sub>2</sub>O

Ciprofloxacin  $\square$  (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid); C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>FO<sub>3</sub> (anhydrous basis); C<sub>17</sub>H<sub>18</sub>N<sub>3</sub>FO<sub>3</sub> x 3.5 H<sub>2</sub>O (3.5 hydrate); 331.4 (anhydrate); 394.3 (3.5 hydrate)



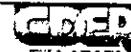
- 3.5H<sub>2</sub>O

## 17. RELATED/SUPPORTING DOCUMENTS:

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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II	Bayer AG	Ciprofloxacin HCl	1	Adequate	20-Aug-2003	N/A
	II	Bayer AG	Ciprofloxacin	1	Adequate	9-Dec-2002	N/A
	III			4	N/A	N/A	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
	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
	III			3	Adequate	6/06/02	Acceptable
	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

<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

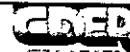
6 – DMF not available

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	61,331	Ciprofloxacin extended-release tablets
NDA	21-473	CIPRO XR Tablets, 500-mg

### 18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	17-Dec-2002	Janine D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Not submitted yet	N/A	N/A
DMETS	N/A	N/A	N/A
EA	Categorical exclusion	N/A	N/A
Microbiology	N/A	N/A	N/A

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# The Chemistry Review for NDA 21-554

## 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, CIPRO I.V., and CIPRO XR tablets, 500-mg).

CIPRO XR tablets contain 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 DMF Type II by Bayer AG. The retest period for the ciprofloxacin hydrochloride drug substance is 12 months.

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

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

## 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 1000 mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin hydrochloride (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (425.2 mg, calculated on the dried basis).

CIPRO XR 500 mg tablets (containing identical active and inactive components) for a once-a-day treatment of uncomplicated urinary tract infections have been approved previously (December 2002) via NDA 21-473.

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

CIPRO XR tablets are available as 1000-mg coated tablets for a once-a-day treatment of complicated urinary tract infections. The tablets are packaged in three packaging configurations, HDPE 250 cc bottles (of 100 tablets), HDPE 150 cc bottles (of 50 tablets), and PVC/PVDC clear blisters with laminated foil backing.

The proposed expiration dating of 24 months as proposed by the applicant for CIPRO XR tablets, 1000 mg 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), 1000-mg. 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 and the 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 (now ODS) and by the Division HFD-590 for NDA 21-473. 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.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

DFS (electronic)

**B. Endorsement Block**

Chemist: Dorota Matecka/08/15/03

Chemistry TL: Norman Schmuff

PM: Jouhayna Saliba

**C. CC Block**

39 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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8/30/03 01:56:44 PM  
CHEMIST