

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-554

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-554

Bayer Pharmaceuticals Corporation
Attention: Andrew Verderame, Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Mr. Verderame:

Please refer to your new drug application (NDA) dated October 29, 2002, received October 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO® XR (ciprofloxacin extended release tablets), 1 gram.

We acknowledge receipt of your submissions dated:

December 13, 2002	March 25, 2003 (2)	June 27, 2003
January 3, 2003	May 2, 2003	July 15, 2003
January 13, 2003	May 9, 2003	July 29, 2003
January 20, 2003	May 30, 2003 (2)	August 5, 2003
January 28, 2003 (2)	June 2, 2003	August 6, 2003
February 14, 2003	June 4, 2003	August 22, 2003
February 20, 2003	June 6, 2003 (2)	August 28, 2003 (2)

This new drug application provides for the use of CIPRO® XR (ciprofloxacin extended release tablets) for complicated urinary tract infections and acute uncomplicated pyelonephritis.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert submitted August 28, 2003) and submitted labeling (immediate container and carton labels submitted October 29, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-554." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated August 28, 2003. These commitments are listed below.

1. Provide confirmative evidence of CIPRO XR efficacy in treating complicated urinary tract infections caused by *P. aeruginosa*.

Protocol Submission:	Within 6 months of the date of this letter
Study Start:	Within 12 months of the date of this letter
Final Report Submission:	Within 39 months of the date of this letter

2. Perform Monte Carlo simulations to obtain steady state estimates of ciprofloxacin systemic exposure after administration of the following regimens. These simulations are to be performed over the ranges of creatinine clearance (CL_{cr}) values specified below for normal renal function and mild, moderate, and severe renal impairment, rather than using a single CL_{cr} value:

- 1000 mg CIPRO[®] XR for 14 days in patients with mild renal impairment (CL_{cr} 50-80 mL/min)
- 1000 mg CIPRO[®] XR for 14 days in patients with moderate renal impairment (CL_{cr} 30-50 mL/min)
- 500 mg CIPRO[®] XR for 14 days in patients with severe renal impairment (CL_{cr} <30 mL/min)
- 500 mg CIPRO[®] XR for 14 days in patients with mild renal impairment (CL_{cr} 50-80 mL/min)
- 500 mg CIPRO[®] XR for 14 days in patients with moderate renal impairment (CL_{cr} 30-50 mL/min)
- 750 mg CIPRO[®] (immediate release) bid for 14 days in patients with normal renal function (CL_{cr} 81-120 mL/min)

Final Report Submission: Within 12 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

FDA's Pediatric Rule at 21 CFR 314.55 was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling.

In addition, submit three copies of the introductory promotional materials that you propose to use for this new strength and new indications. Submit all proposed materials in draft or mock-up form, not

NDA 21-554

Page 3

final print. Send one copy to this division/ the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to NDA 21-473 and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-473 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling and postmarketing study commitment reports requested above.

If you have any questions, call Jouhayna Saliba, Pharm.D., Regulatory Project Manager at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Renata Albrecht
8/28/03 01:28:48 PM
NDA 21-554