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APPLICATION NUMBER:

19-537 / S-049

20-780 / S-013

19-847 / S-027

19-857 / S-031

PHARMACOLOGY REVIEW(S)

CDER STANDARD COVERSHEET

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

sNDA#: 19-537 (049)

Product Name: CIPRO® (Ciprofloxacin Hydrochloride) Tablets

Sponsor: Bayer Pharmaceuticals Corporation

Indication: Complicated Urinary Tract Infection in Pediatric Patients

Division: Special Pathogen and Immunologic Drug Products
HFD-590

Reviewer: Stephen Hundley, Ph.D., DABT
Acting Pharmacology/Toxicology Team Leader, HFD-590

Date: 3/11/04

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1.0 EXECUTIVE SUMMARY

1.1 Recommendations

Recommendation on Approvability:

The sponsor submitted the sNDA in conjunction with a Pediatric Written Request (latest revision -- 9/23/03). Included in the Pediatric Written Request was a juvenile dog arthrotoxicity study that was completed and submitted as a Toxicology Amendment to the sponsor's IND (submission date -- 7/29/03). The arthrotoxicity observed in juvenile dogs in conjunction with the incidence of arthropathy observed in the pediatric clinical studies conducted as part of the Pediatric Written Request, make approval of the pediatric indication for complicated urinary tract infection contingent upon the inclusion of specific language regarding the risk of arthropathy in the Warning section of the product label and the design and implementation of a post-marketing evaluation plan.

Recommendation for Additional Nonclinical Studies:

No additional nonclinical studies are recommended.

Recommendations on Labelling:

The Warning section of the product label should contain language regarding the elevated incidence of arthropathy in pediatric patients treated with ciprofloxacin relative to the comparator drug. A statement regarding the arthrotoxicity observed in juvenile dogs should also be included and reflect information from the juvenile dog arthrotoxicity study conducted under the Pediatric Written Request. The Animal Pharmacology section of the product label should contain information from this juvenile dog arthrotoxicity study and will include an appropriate animal to human dose comparison based upon the proposed dosing regimen for pediatric patients.

1.2 Summary of Nonclinical Findings

Pharmacologic Activity:

The pharmacologic activity of ciprofloxacin was previously described in the initial approved NDA for CIPRO®. Additional discussion of the pharmacological activity and mechanism of action is not needed for this review.

Nonclinical Overview:

The nonclinical toxicological activity of ciprofloxacin was extensively documented in the approval of CIPRO® for indications that include: urinary tract infection; acute uncomplicated cystitis; chronic bacterial prostatitis; lower respiratory tract infection; acute sinusitis; skin and skin structure infections, bone and joint infections; complicated intra-abdominal infections; infectious diarrhea; typhoid fever; uncomplicated cervical and urethral gonorrhea; and inhalational anthrax. Restatement of the nonclinical toxicological profile for ciprofloxacin is not needed for the current submission.

Nonclinical Safety Issues:

As a class, fluoroquinolones produce arthrototoxicity in juvenile dogs following 7 to 14 days of oral dosing. Juvenile dog studies with ciprofloxacin were in the original NDA 19-537 submission and provided clinical and pathological evidence of arthrototoxicity at an oral dose level of 90 mg/kg/day. Pathological evidence of arthrototoxicity was observed at an oral dose level of 30 mg/kg/day. The Clinical and Pharmacology Reviewers concluded that juvenile dog arthrototoxicity needed additional evaluation as the sponsor conducted clinical trials in pediatric patients for potential pediatric indications.

The Pediatric Written Request for ciprofloxacin contained a study request to examine arthrototoxicity in juvenile dogs (males and females) and specifically to address the issues of post-dose recovery and the potential for latent arthrototoxicity as the musculoskeletal system matured. The study conducted by the sponsor examined multiple weight bearing joints during two weeks of dosing with ciprofloxacin at oral dose levels of 10, 30, and 90 mg/kg/day. Recovery and latent arthrototoxicity potential were examined in the recovery groups which were maintained for a period of five dose-free months; a period that covered complete musculoskeletal development.

No evidence (clinical and histopathological) of arthrototoxicity was observed in male and female juvenile dogs dosed for 14 days at the 10 mg/kg/day dose level at the 24-hour post-dosing terminal sacrifice and in male and female dogs held for the 5-month dose-free recovery period. The 30 mg/kg/day dose level did not result in clinical evidence of arthrototoxicity at any time during the study. Half of the juvenile dogs at the terminal sacrifice exhibited gross pathological and/or histopathological evidence of articular cartilage arthrototoxicity. The incidence and severity of the pathological and histopathological observations were reduced but still present in the 5-month post-dose recovery animals. Clinical evidence of arthrototoxicity was observed in 10 of 12 juvenile dogs at the 90 mg/kg/day dose level. These symptoms were resolved by Week 8 (six weeks into the post-dose recovery phase). All juvenile dogs exhibited articular cartilage lesions based upon gross pathology and histopathology at the terminal sacrifice (24 hours following the final dose). Similarly, all animals at the 5-month post-dose recovery sacrifice from the 2-week, 90 mg/kg/day dosing routine exhibited both gross pathological and histopathological evidence of articular cartilage lesions.

These results indicated that at 30 mg/kg/day, subclinical evidence of arthrototoxicity resulted from 14 days of dosing and that these effects, although diminished, were not completely resolved following a 5-month dose-free recovery period. Plasma area under the concentration vs time curve (AUC) data for ciprofloxacin at the 30 mg/kg/day oral dose level to juvenile dogs (32 $\mu\text{g} \cdot \text{hr/ml}$) was similar to the range of ciprofloxacin AUC values generated from pediatric patients at the proposed therapeutic dose level (approximately 20 to 40 $\mu\text{g} \cdot \text{hr/ml}$). The average AUC values resulted in an animal to human dose equivalent ratio of approximately 1.3 (32 $\mu\text{g} \cdot \text{hr/ml}$ / 24 $\mu\text{g} \cdot \text{hr/ml}$). The ratio for the 90 mg/kg/day dose level was approximately 3.5 (85 $\mu\text{g} \cdot \text{hr/ml}$ / 24 $\mu\text{g} \cdot \text{hr/ml}$) while the 10 mg/kg/day ratio was approximately 0.6 (14 $\mu\text{g} \cdot \text{hr/ml}$ / 24 $\mu\text{g} \cdot \text{hr/ml}$).

The safety issue that appears to be more of a concern for pediatric patients than adult patients is subclinical or clinical arthrototoxicity. Ciprofloxacin plasma AUC levels in juvenile dogs at a dose level that resulted in arthrototoxicity were similar to plasma levels generated in pediatric patients at proposed therapeutic doses of ciprofloxacin.

2.0 DRUG HISTORY AND INFORMATION

sNDA: 19-537
Sequence: 049
Review Number: 1
Submission Type: SE 5
Date of Submission: 9/24/03
Information to Sponsor: Yes (x) No ()

Sponsor: Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175

Manufacturer of Drug Substance: Bayer AG

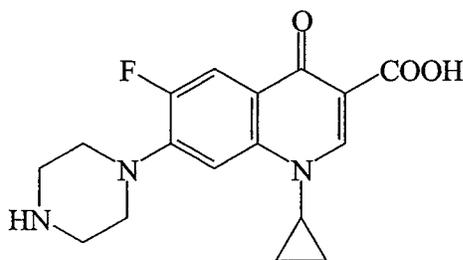
Reviewer: Stephen G. Hundley, Ph.D, DABT
Pharmacology/Toxicology Reviewer

Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 3/11/04

Drug Information

Trade Name: CIPRO® (Ciprofloxacin Hydrochloride) Tablets
Generic Name: Ciprofloxacin HCl
Code Name: Not Applicable
Chemical Name: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[1-piperazinyl]-3-quinoline-carboxylic acid
CAS#: 85721-33-1
Molecular Formula: C₁₇H₁₈FN₃O₃
Molecular Weight: 331.4 (385.8 for the monochloride monohydrate salt)
Molecular Structure:



Relevant Submissions: NDA's: 19-847; 19-857; 20-780; 21-437; 21-554

Drug Class: Antimicrobial Fluoroquinolone

Indication: Complicated Urinary Tract Infection

Clinical Formulation: Tablet

Route of Administration: Oral

Proposed Use: 10 to 20 mg/kg oral doses bid (12 hours) not to exceed ~~daily~~
daily

Studies reviewed for this submission:

Subacute Oral Toxicity Study in Beagle Pups (2-Week Oral Gavage Study + 5-Month Recovery Period), Study No. T 4071448 (Report No. PH-328670).

This study was submitted to IND 21,804 on 7/29/03; a Pharmacology/Toxicology Review and Evaluation was completed on 8/19/03.

No additional nonclinical studies were submitted for review in support of this sNDA submission.

3.0 CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

The following observations resulted from the juvenile dog arthrotoxicity study:

- Clinical evidence of arthrotoxicity was only observed at the 90 mg/kg/day dose level and was resolved by the sixth week following the termination of dosing.
- Gross pathological and histopathological evidence of articular cartilage toxicity was observed at the 30 and 90 mg/kg/day dose levels and persisted to the 5-month post-dosing recovery sacrifice.
- The severity of the articular cartilage pathology and histopathology did not increase during the musculoskeletal maturation period for beagle dogs dosed at the 90 mg/kg/day dose level and diminished in severity for the 30 mg/kg/day group.
- The 10 mg/kg/day dose level was the no-effect level for articular cartilage toxicity and there was no indication that this dose level predisposed immature beagle dogs to develop histopathological or ultrastructural (electron microscopy) evidence of arthrotoxicity during musculoskeletal maturation.
- Ciprofloxacin plasma AUC levels at the 30 mg/kg/day dose level were similar to plasma AUC levels observed in pediatric patients at proposed therapeutic levels of ciprofloxacin.

The juvenile dog arthrotoxicity study conducted by the sponsor satisfied the study requirements outlined in the Pediatric Written Request. This study demonstrated a definitive dose response for the severity of arthrotoxicity. Gross pathological and histopathological lesions to articular cartilage in weight bearing joints were not resolved during the 5-month post-dosing period during which full musculoskeletal development occurs in beagle dogs. The observations from the juvenile dog arthrotoxicity study suggest that pediatric patients may experience a greater incidence of adverse events associated with arthrotoxicity than has been observed with adult patients.

3.2 Recommendations

The arthrotoxicity observed in juvenile dogs in conjunction with the incidence of arthropathy observed in the pediatric clinical studies (described in the Medical Officer's Review) make Pharmacology/Toxicology approval of the pediatric indication for complicated urinary tract infection contingent upon the inclusion of specific language in

the Warning section of the product label regarding the risk of arthropathy to pediatric patients and the design of a post-marketing safety evaluation plan approved by the Division of Special Pathogen and Immunologic Drug Products.

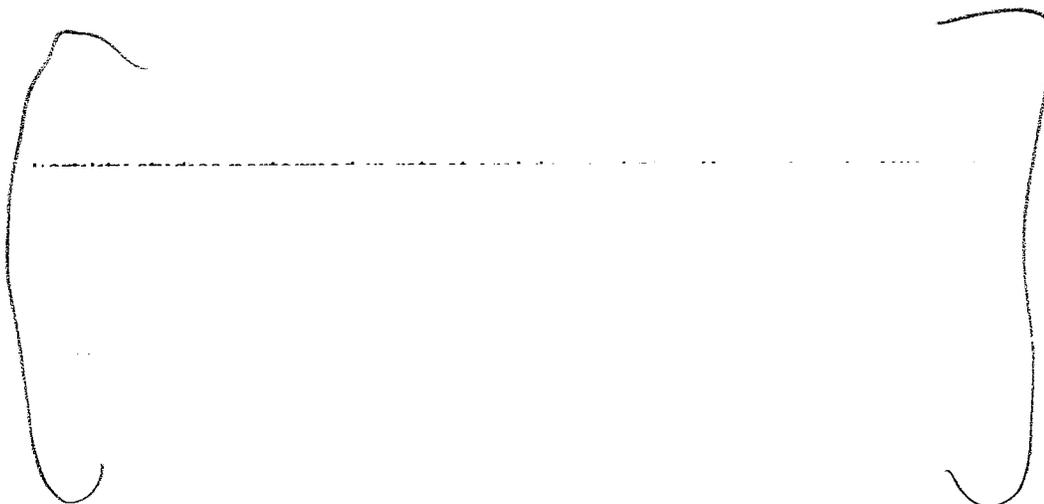
3.3 Suggested Labelling

Language proposed by the Medical Officer for the Warning section of the product label:



The following proposed labelling changes by the Pharmacology/Toxicology Reveiwer are not necessarily related to the current submission but reflect an update to the overall ciprofloxacin label by introducing animal to human dose equivalents based on body surface area conversions or plasma AUC comparisons.

Carcinogenesis, Mutagenesis, Impairment of Fertility



level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed (See **Warnings**).

ANIMAL PHARMACOLOGY



The remaining nonclinical toxicology language in the ciprofloxacin product label proposed by the sponsor appear to be appropriate. (Note: sentences in *italics* appear in the current CIPRO® label in the **ANIMAL PHARMACOLOGY** section and will remain unchanged.)

Stephen G. Hundley, Ph.D., DABT
Acting Team Leader & Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products
HFD-590

Concurrence:

Steve Gitterman, MD
Deputy Division Director
Division of Special Pathogen and Immunologic Drug Products
HFD-590

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

Steve Hundley
3/18/04 08:12:12 AM
PHARMACOLOGIST

Steven Gitterman
3/19/04 04:25:59 PM
MEDICAL OFFICER