CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-537/S038

19-847/S024

19-857/S027

19-858/S021

20-780/S008

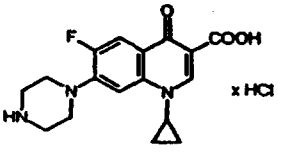
PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Ciprofloxacin, monkey study, anthrax, bioterrorism
Reviewer Name: Terry S. Peters, D.V.M.
Division Name: Anti-Infective Drug Products
HFD #: 520
Review Completion Date: 6/30/00
IND/NDA number: NDA 19-537
Sponsor (or agent): Bayer Corporation, West Haven, CT
Contact person: Andrew S. Verderame, (203) 812-5172
Drug:

Generic Name: Ciprofloxacin hydrochloride
Trade Name: Cipro®
Chemical Name: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid monohydrochloride, monohydrate

Structure:



Ciprofloxacin Hydrochloride

Relevant INDs/NDAs/DMFs: NDA 19-847, 19-857, 19-858, 20-780

Drug Class: Quinolone

Indication: Post-exposure prophylaxis for anthrax

Clinical formulation: Tablets

Route of administration: Oral

Proposed clinical protocol or Use: 500 mg q 12 hrs for 60 days

Studies reviewed within this submission:
Efficacy of antibiotic treatment and vaccination in protection of rhesus monkeys following aerosol infection with *Bacillus anthracis*, by principal investigator Col. A.M. Friedlander

Scientific literature reviewed: Yes

TOXICOLOGY:

General Comments: This study was conducted to determine the effect of doxycycline with /without MDPH (human anthrax vaccine), and two other antibiotics in the treatment of monkeys following aerosol exposure to anthrax spores. It was a three part study: 1) determine the LD_{50} for anthrax spores to 2 rhesus monkeys, 2) uninfected monkeys given doses of the test antibiotics (doxycycline, penicillin, ciprofloxacin) to

determine serum drug levels, and 3) monkeys exposed to the LD_{50} of anthrax spores and treated with vaccine and/or a therapeutic dose of antibiotic.

Study No: Protocol B90-06
Conducting laboratory and location: [redacted]

Date of study initiation: 9/10/90
GLP compliance: No, but not necessary
QA- Report: No
Methods:
Dosing:

- species/strain: Adult rhesus monkeys (Macaca mulatta)
- #/sex/group or time point: 2 monkeys Part I, 6 monkeys Part II, 10/group Part III; sex not specified but majority were male. Two survivors/group were to be euthanized and necropsied at the end of the experiment to determine the presence of viable spores. This was not done. Five additional control animals were added to the rechallenge portion of the study as all of the original controls died.
- age: Adult, specifics unknown
- weight: 5-13 kg
- dosage groups in administered units: *Bacillus anthracis* at ~2.5x 10^5 spores (50-100x the LD50) [both values calculated by the sponsor] of strain Vollum 1B on Day 0; Penicillin G i.m. at 180,000 units q 12 h, doxycycline at 30 mg by nasogastric tube q 12 h, or ciprofloxacin 125 mg by nasogastric tube q 12 h for 30 days; MDPH alone on Days 1 and 14 post-exposure; MDPH + doxycycline; saline alone i.m. Antibiotics were started on Day 1 and on the first day, the doses of Cipro and doxycycline were 2x.

Spore exposure: Using a DeVilbiss nebulizer as a head-only exposure chamber for 10 minute exposure and 5 minute 'air wash' before removing monkeys from the chamber.
Drug, lot: Not specified
Observations and times:

- Clinical signs: Observation daily. Monkeys were injected with Telazol (tiletamine/zolazepam) [eliciting deep sedation/anesthesia] for all nasogastric dosing (twice/day for Cipro and doxycycline groups), and blood collections.
- Body weights: Not performed
- Food consumption: Not performed
- Ophthalmoscopy: Not performed
- EKG: Not performed
- Hematology: Part I: pre-exposure and daily thereafter for culture, immunology and hematology and clinical chemistries; Part II: none; Part III controls: Daily cultures, q 48 hrs for chemistries, Ag/Ab, drug trough levels, hematology, FDP, PTT, PT and Days 5 and 9 for peak drug levels until 80% of controls died. Thereafter, twice weekly sampling was done.
- Urinalysis: Not performed
- Gross pathology: All animals had limited necropsies that included blood cultures, chemistries, blood smear stained for bacilli, FDP, PT and PTT.
- Organs weighed: Not performed
- Histopathology: Part I: intrathoracic lymph node, spleen, lung, liver, brain and kidney only; Part II- no histology; Part III: as in Part I
- Toxicokinetics: Part II only for serum drug levels on Days 1 and 2 following antibiotic administration and for serum bactericidal levels against Vollum IB strain of *B. anthracis*. Data reviewed by HFD-550.
- Other: Rechallenge: At the end of Part III, 2 surviving monkeys/group were to be euthanized and necropsied to determine presence of viable spores. Remaining monkeys were rechallenged with 100 LD_{50} of spores. Due to the death loss, all surviving animals were rechallenged at 30 days after the end of the antibiotic regimen.

Results:

- If the animal survived the original challenge and rechallenge, it was not euthanized but was "maintained for other protocols if appropriate." An unusual comment in the histopathology

sheet for L62 (unvaccinated, penicillin-treated animal) was: "Antibiotic was administered twice daily for 30 days under Telazol anesthesia (3 mg/kg) via gastric tube." The protocol stated that penicillin could be given i.m. and shouldn't have necessitated anesthesia.

The data from the 1st exposure is supportable (up to 60 days post-inhalation) but no raw data (aside from the table on page 61 of volume 2) are presented for the rechallenge animals.

Monkey #	Group Day of death (1st or 2nd exp)	Survival	Bacteremia (1st exposure) *^	Blood Culture Positive (Investig)**	Survival post-rechallenge	Bacteremia 2nd exposure (investig.)	Bacillemia (histo. Sheets)
837T	Control Day 3[1]	Dead	No comment	Yes			Severe
47G	Day 5[1]	Dead	No comment	Yes			Severe
3JH	Day 7[1]	Dead	No comment	Yes			No histo.
D274	Day 8[1]	Dead	No comment	Yes			Mild
128N	Day 4[1]	Dead	No comment	Yes			Severe
981C	Day 5[1]	Dead	No comment	Yes			Moderate
84A44	Day 5[1]	Dead	No comment	Yes			Moderate
A027	Day 6[1]	Dead	No comment	Yes			Moderate
3LP	Day 7[1]	Dead	No comment	Yes			Marked
3N1	Day 6[2]	Surv.	No comment	No	Dead		Mild-severe
B27^	??			N.D.			No histo.
I371^	Day 5[2]			N.D.	Dead		Mild-marked
H560^	Day 3[2]			N.D.	Dead		Mild-marked
B24^	Day 31[2]			N.D.	Dead		Mild-marked
B6577^	Day 6[2]			N.D.	Dead		Moderate-marked
1633	Vaccine Day 5[1]	Dead	No comment	Yes			Moderate
C380	Day 5[1]	Dead	No comment	Yes			Minimal-mild
4BD	Day 7[1]	Dead	No comment	Yes			Moderate
H-981C	Day 5[1]	Dead	No comment	Yes			No histo
85340	Day 6[1]	Dead	No comment	Yes			Moderate
1623	Day 10[1]	Dead	No comment	Yes			Moderate
T34	Day 10[1]	Dead	No comment	Yes			Mild
468C	Day 8[1]	Dead	No comment	Yes			Mild-severe
023E		Surv.	No comment	No	Surv.		No histo.
85415		Surv.	No comment	Neg. before death *	Surv.		No histo.
85265	Pen. Day 4[2]	Surv.	No comment	No	Dead	Yes	Mild
349D	Day 3[2]	Surv.	No comment	No	Dead	Yes	Mild-moderate
18386	Day 6[2]	Surv.	No comment	No	Dead	Yes	Mild
446C	Day 4[2]	Surv.	No comment	No	Dead	Yes	Moderate-severe
H-T324	Day 8[2]	Surv.	No comment	No	Dead	Yes	Mild-marked
B748	Day 6[2]	Surv.	No comment	No	Dead	Yes	Mild-marked
927C	Day 6[2]	Surv.	No comment	No	Dead	Yes	Mild
C532	Day 39[1]	Dead	Yes	Yes			Moderate
088CC	Day 42[1]	Dead	Yes	Yes			Moderate
L62	Day 50[1]	Dead	Yes	Yes			Moderate

45N	Doxy Day 3[2]	Surv.	No comment	No	Dead	Yes	Mild-moderate
45W	Day 5[2]	Surv.	No comment	No	Dead	Yes	Moderate-severe
DA143	Day 5[2]	Surv.	No comment	No	Dead	Yes	Moderate-severe
D625	Day 4[2]	Surv.	No comment	No	Dead	Yes	Moderate-severe
18434	Day 4[2]	Surv.	No comment	No	Dead	Yes	Mild-severe
461	Day 8[2]	Surv.	No comment	No	Dead	Yes	Minimal
13379	Day 5[2]	Surv.	No comment	No	Dead	Yes	Mild-marked
83A01	Day 6[2]	Surv.	No comment	No	Dead	Yes	Mild-moderate
969C/40W	Day 4[2]	Surv.	No comment	No	Dead	Yes	Mild-marked
396D	Day 58[1]	Dead	Yes	No		Yes	Mild-moderate
358D	Cipro Day 3[2]	Surv.	No comment	No	Dead	Yes	Mild-severe
82A35	Day 3[2]	Surv.	No comment	No	Dead	Yes	Mild-severe
410D	Day 5[2]	Surv.	No comment	No	Dead	Yes	Mod-severe
A32	Day 3[2]	Surv.	No comment	No	Dead	Yes	Mild-severe
45Y	Day6[2]	Surv.	No comment	No	Dead	Yes	Mild
40B	Day 10[2]	Surv.	No comment	No	Dead	Yes	Mild-moder
T292		Dead	Accid. Death	No			No
T308	Day 36[1]	Dead	No comment	No	Dead	Yes	Mild-moder
B7388	Day 103[1]	Surv.	Urin. dysfunc	No	Dead		No comment
84456A		Surv.	No comment	No	Surv.		No histo.
H538	Doxy+MDPH	Dead	No comment	No		No	No- myocard. Failure
380D		Surv.	No comment	No	Surv.	No	No histo.
85331		Surv.	No comment	No	Surv.	No	No histo.
H-A958		Surv.	No comment	No	Surv.	No	No histo.
T313		Surv.	No comment	No	Surv.	No	No histo.
H-05		Surv.	No comment	No	Surv.	No	No histo.
155DA		Surv.	No comment	No	Surv.	No	No histo.
85278		Surv.	No comment	No	Surv.	No	No histo.
A183		Surv.	No comment	No	Surv.	No	No histo.
3EX		Surv.	No comment	No	Surv.	No	No histo.

- ^ Animals added to the rechallenge portion of the study, not part of the original 10/dose group
- *Animal was culture positive but returned to negative status before death
- ## Animal was considered a survivor by the investigator. However, the individual histopathology sheet for this animal concludes with: " All gross observations and light microscopic findings in this animal are considered to be consistent with an etiologic diagnosis of systemic anthrax." No bacillemia was reported. Therefore, this animal's information should not be included in the calculations for this study.
- ** Invest.= investigator-derived from the data for first 30 days on study
- *** Histo. Sheets= data derived from individual animal histopathology sheets for animals that died anytime during the study
- *^ Section left blank in submission on page 61 of volume 2

- Body weights: No significant treatment-related findings were reported
  Hematology: No significant treatment-related findings were reported

- Clinical chemistry: No significant treatment-related findings were reported
- Organ Weights: Not taken
- Gross pathology: Lesions reported with consistency across dose groups included: enlarged mesenteric and/or thoracic lymph nodes, discolored lungs, splenic enlargement with/without congestion, mediastinal edema, occasional subarachnoid congestion and/or hemorrhage, meningitis with/without hemorrhage
- Histopathology

An. #	Group	Survival	Lesion Lung	Spleen	Liver	LN	Bacillemia
837 T	Control	Dead	Edema, minimal	Hemorr., severe	Hypertrophy, moder.	Histiocytosis, severe	Yes- severe
47G		Dead	No sign. comment	Splenitis, mild	No comment	Lymphadenitis, mild-moderate	Yes- severe
3JH		Dead	No histo				
D27 4		Dead	No sign. Comment	Splenitis, mild	Hypertrophy, moder.	Lymphadenitis, necrotiz., mild	Yes- mild
128 N		Dead	Fibrinohemorr. Pneu. Severe	Congestion severe	Hypertrophy, severe	Histiocytosis, moderate	Yes- severe
981 C		Dead	Necrosupp. Pneu., sev.	Lymphoid depletion, moderate	Hepatitis, focal	Edema, moderate & hemorrhage, marked	Yes- moderate
84A 44		Dead	Hemorr. & edema, marked	Lymphoid depletion, marked	Necrosis, mild	Atrophy, moderate	Yes- moderate
A02 7		Dead	Hemorrh., moderate	Lymphoid depletion, marked	No comment	Hemorrh., mod., lymphoid depletion, mod.	Yes- moderate
3LP		Dead	No sign. comment	Lymphoid depletion, severe, hemorr., sev.	Bacilli	Fibrinohemorr. lymphadenitis, moderate	Yes- marked
3N1		Surv.	Pneu, sev. with edema	Necrohemorr splenitis, severe	Hepatitis, mild	Atrophy, moderate with edema	Yes- mild-severe
B27			No histo				
1371			Pneu., moderate	Necrotizing splenitis, marked	Congestion, marked	Necrotizing lymphadenitis, severe	Yes- mild-marked
H56 0			Hemorr. & edema, mod.	Suppur. splenitis, severe	Hepatitis, mild	Necrohemorr lymphadenitis, severe	Yes- mild-marked
B24			Pneu., moderate; hemorr., sev.	Necrohemorr splenitis, severe	Congestion marked	Atrophy, moderate	Yes- mild-marked
B65 77			Edema, severe	Necrohemorr splenitis, severe	Congestion mild	Atrophy, mild	Yes- moderate-marked
1633	Vaccine	Dead	Pneu., mild	Necrohemorr	Congestion	Lymphoid	Yes-

			with edema	splenitis, severe	severe	necrosis & depletion, severe, Hemorr., severe	moderate
C380		Dead	Anthrasilicosis, min.	Necrohemorr splenitis, severe	Degener. & necrosis, severe	Lymphoid necrosis & depletion, severe with edema	Yes-minimal-mild
4BD		Dead	Edema & pneu, mod.	Hemorr., mod., mild splenitis	Necrosis, mild- mod.	Necrohemorr lymphadenitis, severe	Yes-moderate
H981C		Dead	No histo				
853410		Dead	Edema, mild	Lymphoid depletion, moderate	Necrosis, mod.	Hemorr. & edema, moder.; atrophy, moder.	Yes-moderate
1623		Dead	Edema, mild	Lymphoid necrosis & depletion, severe, hem	Edema, mild	Histiocytosis, mild	Yes-moderate
T34		Dead	Edema, mild	Lymphoid necrosis & depletion, severe, hem	Edema, mild	Lymphoid necrosis & depletion, severe, hemorrhage	Yes- mild
468C		Dead	Pneu., necrohem., moderate	Necrohemorr splenitis, severe	Congestion, moderate	Necrohemorr lymphadenitis, severe	Yes- mild-severe
023E		Surv.	No histo				
85415		Surv.	No histo				
85265	Pen.	Surv.	Mild pneu.	Sev. Congestion	Sev. Congestion	Necrohemorr lymphaden. sev.	Yes- mild
349D		Surv.	Congestion, marked	Necrohemorr splenitis, severe	Mod. Congestion	Mod. Congestion	Yes- mild-moderate
18386		Surv.	Congestion marked, mild pneu	Necrohemorr splenitis, severe	Necrobiosis	Atrophy, moderate	Yes- mild
446C		Surv.	Mild pneu., hemorrhage	Necrohemorr splenitis, severe	Sev. Congestion	Necrohemorr lymphadenitis, severe	Yes-moderate-severe
H-T324		Surv.	Mild pneu., mod. cong.	Splenitis, marked, hemorr.	Mod. congestion	Atrophy, marked	Yes- mild-marked
B748		Surv.	Mod. congestion	Necrohemorr splenitis,	Mod. congestion	Atrophy, moderate	Yes- mild-marked

				severe			
927 C		Surv.	Marked pneu, congest. severe	Necrotizing splenitis, moderate	Mod. congestion	Marked congestion	Yes- mild
C53 2		Dead	Hemorrh., mod-sev.	Splenitis, moderate	Congestion, mild	Anthrasilicosis	Yes- moderate
088 CC		Dead	No comment	Necrotizing splenitis, mod.	Degener & necrosis, minimal	Lymphoid depletion, mild	Yes- moderate
L62		Dead	Mild hemorr.	Necrohemorr splenitis, moderate	Sev. Congestion	Lymphoid depletion, moderate	Yes- moderate
45N	Doxy	Surv.	MF edema, mild-mod	Hemorr, severe	Congestion, moderate	Atrophy, severe	Yes- mild-moderate
45W		Surv.	Mod. pneu	Necrohemorr splenitis, severe	Congestion, moderate	Marked congestion	Yes- moderate-severe
DA143		Surv.	Mod-sev. Pneu & hemorr.	Necrohemorr splenitis, severe	Congestion, marked	Necrohemorr lymphadenitis, severe	Yes- moderate-severe
D625		Surv.	Mild pneu.	Necrohemorr splenitis, severe	Congestion, marked	Congestion, marked; necrohemorr. lymphadenitis, moderate; atrophy, mild	Yes- moderate-marked
18434		Surv.	Marked bacillemia	Necrohemorr splenitis, severe	Mild hepatitis	Necrotizing lymphadenitis	Yes- mild-severe
46I		Surv.	Mild pneu., diffuse congestion	Suppur. splenitis, severe	Congestion, moderate	Vasculitis, acute	Yes- minimal
13379		Surv.	Mod. pneu, diffuse congestion	Necrohemorr splenitis, severe	Congestion marked	Necrohemorr lymphadenitis, marked; atrophy, mild	Yes- mild-marked
83A01		Surv.	Marked congestion, hemorr.	Necrohemorr splenitis, severe	Congestion severe	Congestion, marked	Yes- mild-moderate
969 C/40 W		Surv.	Marked congestion	Necrohemorr splenitis, severe	Congestion severe	Mod. histiocytosis	Yes- mild-marked
396 D		Dead-meningitis, sev.	No comment	Necrotizing splenitis, severe	Degener. & necrosis, severe	Mod. histiocytosis	Yes- mild-moderate
358 D	Cipro	Surv.	Mild congestion	Necrohemorr splenitis, severe	Congestion mild	Necrotizing lymphadenitis, moderate	Yes- mild-severe
82A35		Surv.	Marked congestion	Necrohemorr splenitis, severe	Congestion mild	Atrophy, mild-moderate	Yes- mild-severe
410 D		Surv.	Mild-sev. Pneu.	Necrotizing splenitis, marked	Congestion severe	Necrohemorr lymphadenitis, severe; atrophy,mild	Yes- mod.-severe

A32		Surv.	Mild congestion	Necrohemorr splenitis, severe	Congestion severe	Necrotizing lymphadeniti s, mild; atrophy,mild	Yes- mild-severe
45Y		Surv.	Mod. pneu., marked congestion	Necrohemorr splenitis, marked	Congestion moderate	Necrohemorr lymphadeniti s, severe	Yes- mild
40B		Surv.	Mod. congestion	Necrohemorr splenitis, moderate	Congestion moderate	No comment	Yes- mild-moderate
T29 2		Dead- Not consist with anthrax	Necrohem. Pneu., marked	Lymphoid depletion, marked	Vacuolar change	Histiocytosis, mild	No- not consistent with anthrax
T30 8		Dead	Edema, congestion, severe	Necrohemorr splenitis, marked	Edema, mild	Histiocytosis, mild	Yes- mild-moderate
B73 88		Surv.- ##	Brochiolitis mild	Splenitis, mild; lymphoid depletion, marked	No comment	Lymphoid depletion, moderate	No comment-urinary dysfunction
8445 6A		Surv.	No histo				
H53 8	Doxy+ MDPH	Dead	Congestion moderate	Congestion mild	Edema, mild	Lymphoid depletion, mild	No-myocardial failure
330 D		Surv.	No histo				
8533 1		Surv.	No histo				
H-A95 8		Surv.	No histo				
T31 3		Surv.	No histo				
H-05		Surv.	No histo				
155 DA		Surv.	No histo				
8527 8		Surv.	No histo				
A18 3		Surv.	No histo				
3EX		Surv.	No histo				

- ## Animal was considered a survivor by the investigator. However, the individual histopathology sheet for this animal concludes with: " All gross observations and light microscopic findings in this animal are considered to be consistent with an etiologic diagnosis of systemic anthrax." No bacillemia was reported. These statements are contradictory. Therefore, this animal's information should not be included in the calculations for this study.

Summary of Histologic Findings in Monkeys Challenged Once with B. anthracis by Inhalation*

Group	Control	Vaccine	Penicillin	Doxycycline	Ciprofloxacin
Lung					
No histo/no sign. findings	4/8	1/7	1/3	1/1	0/1
Hemorr &/or edema	2/8	4/7 (mild)	2/3	0/1	1/1
Pneumonia	2/8	3/7	1/3	0/1	0/1
Spleen					
No histo/no sign. findings	0/8	0/7	0/3	0/1	0/1
Hemorrhage	2/8	1/7	0/3	0/1	0/1
Splenitis	2/8 (mild)	6/7	3/3	1/1	1/1
Lymphoid depletion	4/8	3/7	0/3	0/1	0/1
Lymph node					
No histo/no sign. findings	0/8	0/7	1/3	0/1	0/1
Lymphadenitis	6/8	3/7	0/3	1/1	1/1
Atrophy	1/8	1/7	0/3	0/1	0/1
Necrosis &/or depletion	1/8	3/7	2/3	0/1	0/1

Overall Summary of Histologic Findings in Monkeys Challenged with B. anthracis by Inhalation*

Group	Control	Vaccine	Penicillin	Doxycycline	Ciprofloxacin
Lung					
No histo/no sign. findings	5/13	3/7	1/10	2/10	1/8
Hemorr &/or edema	5/13	4/7	6/10	5/10	6/8
Pneumonia	5/13	2/7	3/10	3/10	1/8
Spleen					
No histo/no sign. findings	2/13	2/7	0/10	0/10	1/8
Hemorrhage	2/13	1/7	1/10	1/10	0/8
Splenitis	7/13	3/7	9/10	9/10	7/8
Lymphoid depletion	4/13	3/7	0/10	0/10	0/8
Lymph node					
No histo/no sign. findings	1/13	3/7	2/10	3/10	2/8
Lymphadenitis	7/13	3/7	2/10	3/10	4/8
Atrophy	4/13	1/7	3/10	3/10	3/8
Necrosis &/or depletion	1/13	3/7	2/10	0/10	0/8

* If the numbers in the denominator are <10, the survivors are excluded from the table as no necropsy was performed on these animals except for the 2 animals from the ciprofloxacin arm that (in the opinion of this reviewer) should not be included in the data tables. Two of the dead animals from the control arm did not have histopathology performed on their tissues.

- Toxicokinetics: Reviewed by HFD-550

Internal comments:

In Smith, Jones and Hunt, Veterinary Pathology, they state: "The microscopic findings in generalized cases are dominated by the presence of large numbers of anthrax bacilli in the blood and most other tissues. These large rod-shaped organisms can be demonstrated in smears or tissue sections, but they cannot be distinguished from saprophytic bacilli without culturing them and determining their pathogenicity in laboratory animals." As the majority of the antibiotic-treated animals in this study did not have culturable organisms in their blood but did have bacillemia, it is difficult to definitively assign the cause of death *to B. anthracis* infection using these criteria. To make the diagnosis definitive, it would have been advisable to inject blood from affected monkeys into mice and determine lethality. Additional special stains to confirm the bacillemia as due to *B. anthracis* would also have been illustrative.

The summary table for the histologic lesions demonstrates no clear cut advantage to any specific antimicrobial therapy to animals administered *B. anthracis* by the inhalation route.

Reviewer signature: /S/

cc: list
HFD-550/Orig. NDA
HFD-550/MO/Meyerhoff
HFD-550/PT/Hundley/Hastings
HFD-520/PT/Peters
HFD-550/DivDir/Albrecht
HFD-550/CSO/Jensen
ODE IV/Murphy
Draft date (# of drafts): 1; 6/30/00

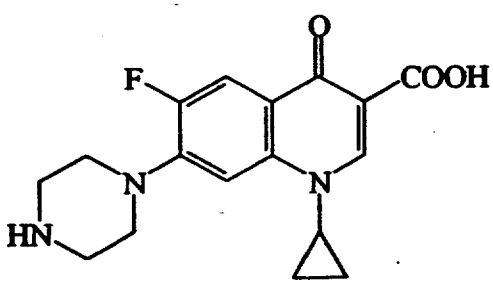
Concurrence Only:
HFD-520/DepDivDir/Gavrilovich /S/ 8/16/2000
HFD-520/DivDir/Chikami
HFD-520/PTTeamLdr/Ost... /S/ 7/10/00

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

NDA's#:	19-537, 20-780, 19-857, 19-858, & 19-847
Serial Number:	SLR's 038, 008, 027, 021, & 024, respectively
Type:	Supplemental New Drug Application
Date of Submission:	3/1/00 & 3/2/00
Review Division:	Special Pathogen and Immunologic Drug Products HFD – 590
Reviewer:	Stephen G. Hundley, Ph.D., Pharmacologist
Review Completion Date:	8/7/00
Sponsor:	Bayer Corporation 400 Morgan Lane West Haven, CT 06516 – 4175
Phone:	203 – 812 – 5172

Drug Information

Name:	Ciprofloxacin
Drug Name:	CIPRO®
Chemical Name:	1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[1-piperazinyl] -3-quinoline-carboxylic acid
CAS#:	85721-33-1
Molecular Formula:	$C_{17}H_{18}FN_3O_3$
Molecular Weight:	331.4 (385.8 for the monochloride monohydrate salt)
Molecular Structure:	



Drug Category:	Anitmicrobial – Fluoroquinolone
Related Submissions:	IND [redacted]
Proposed Indication:	Prophylaxis for Inhalational Anthrax Exposure

BACKGROUND

Ciprofloxacin is a fluoroquinolone approved for use as a broad-spectrum antibacterial agent. Current approved uses for the tablet, oral suspension, and IV forms include; acute sinusitis, lower respiratory tract infections, acute exacerbation of chronic bronchitis, urinary tract infection, acute uncomplicated cystitis, chronic bacteria prostatitis, complicated intra-abdominal infections, skin and skin structure infections, bone and joint infections, infectious diarrhea, typhoid fever, and uncomplicated cervical and urethral gonorrhea. The current supplemental NDA submission is to support an indication for prophylaxis to inhalational Anthrax exposure.

The sponsor was encouraged by different federal agencies to seek an indication for prophylaxis treatment for inhalational exposure to Anthrax spores. There is governmental concern about potential bioterrorism acts that may include airborne dispersal of Anthrax spores in metropolitan areas. Ciprofloxacin could be a viable alternative to penicillin and doxycycline, particulary if Anthrax strains resistant to these two compounds are used. The proposed oral dosing regimen for Anthrax prophylaxis is 500 mg orally twice a day (every 12 hours) for a period of 60 days. Intravenous therapy would include 60 min. infusions of 400 mg of ciprofloxacin *iv* formulation every 12 hours followed by conversion to oral dosing. The proposed oral dosing therapy for children is 10 to 15 mg/kg every 12 hours (not to exceed 500 mg per dose). The proposed *iv* therapy for children is also 10 to 15 mg/kg every 12 hours (not to exceed 400 mg per dose).

The sponsor submitted several literature articles dealing with Anthrax and treatment of Anthrax. No studies were conducted by the sponsor in support of this submission. None of the literature articles contained material for pharmacology/toxicology review and evaluation. One research study was obtained by the sponsor under an agreement with the [redacted] The study entitled "Efficacy of Antibiotic Treatment and Vaccination in Protection of Rhesus Monkeys Following Aerosol Infection with *Bacillus anthracis*" was the only study submitted in support of the efficacy of ciprofloxacin in post-inhalational Anthrax prophylaxis. There are no clinical studies conducted with humans for obvious ethical reasons, therefore the rhesus monkey model served as a surrogate for human exposure. This study was reviewed in depth by the Medical Officer and the Biopharmaceutical, and Microbiological Reviewers. In addition, the report was reviewed by a D.V.M. Pathologist. The Pharmacology/Toxicology review only examines a few selected areas of the study report.

Nonclinical Study Review

Efficacy of Antibiotic Treatment and Vaccination in Protection of Rhesus Monkeys Following Aerosol Infection with Bacillus anthracis. [redacted]

The study was designed to evaluate the efficacy of penicillin, doxycycline, ciprofloxacin, and doxycycline plus Anthrax vaccine in the prophylaxis of Anthrax following inhalation

exposures. Each exposure routine (including a control group receiving no therapy) consisted of ten adult rhesus monkeys of which 8 or 9 of each group were males. Ages varied and weights ranged from 5 to 13 kg. Each monkey received a single 10 minute head-only exposure to Anthrax spores. The airborne concentrations of spores were generated by a [redacted]

Monkeys received from 5 to 10 LD_{50}'s of the Anthrax spores (based upon historical LD_{50} values for rhesus monkeys). Monkeys were anesthetized and received ciprofloxacin via nasogastric tubes. The dosing routine was 125 mg of ciprofloxacin at 12 hour intervals (twice daily dosing) for a period of 30 days after exposure to Anthrax spores. The weights of the monkeys receiving the ciprofloxacin treatment ranged from 6.1 to 10.2 kg and the average daily dose level was approximately 32 mg/kg (250 mg daily). The pharmacology/toxicology issue was whether ciprofloxacin at this dose level might result in toxicity. Rhesus monkey toxicity studies were submitted to the original ciprofloxacin NDA's (19-537 and 19-847). Three-month toxicity studies where the highest oral dose was 135 mg/kg resulted in only minimal inflammation in the distal tubules of the kidneys; no effects were observed at the other dose levels (15 and 45 mg/kg). Similar results were observed in a 6-month oral toxicity study at 90 mg/kg. Based upon these results, the ciprofloxacin dose level used in the Anthrax study was unlikely to produce any observable effects. In fact, no observed toxicity was reported in the ciprofloxacin – dosed monkeys during the 30-day dosing period following the Anthrax exposure. One animal died due to dosing error and an additional animal was sacrificed *in extremis* due to urethral obstruction approximately 73 days after the termination of ciprofloxacin dosing. No effects related to ciprofloxacin were observed during the study. Ciprofloxacin was as effective as penicillin and doxycline in providing prophylaxis against Anthrax following inhalation exposure to Anthrax spores.

EVALUATION AND CONCLUSIONS

Definitive and detailed reviews of the rhesus monkey inhalational Anthrax exposure study were done by the Medical Officer and the Biopharm., Microbiology, and D.V.M. Pathology Reviewers. The ciprofloxacin dose level in this study did not produce any toxicological effects that interfered with the interpretation of the study results regarding efficacy of ciprofloxacin in the prophylaxis of Anthrax infection following inhalation exposure to Anthrax spores.

There are no pharmacology/toxicology issues with the proposed ciprofloxacin dose level of 500 mg every 12 hours. The ciprofloxacin dosing of 125 mg twice daily to monkeys is equivalent, based upon relative body surface area, to the proposed human regimen. Additionally, the approved dosing regimen for complicated bone and joint infection is 750 mg b.i.d. for up to 6 weeks and the sponsor provided clinical trial data for neutropenia, osteomyelitis, and UTI prophylaxis that extended the 750 mg b.i.d. dosing for an average of 80 days.