CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-369

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-369

Andrea B. Weir, Ph.D.
Reviewing Pharmacologist

ORIGINAL SUMMARY:

SUBMISSION DATE: September 2, 1997
CENTER RECEIPT DATE: September 8, 1997
REVIEWER RECEIPT DATE: October 15, 1997
DRAFT REVIEW COMPLETE: November 3, 1997

SPONSOR: Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2099

DRUG: CILOXAN (ciprofloxacin hydrochloride ophthalmic ointment)

PHARMACOLOGICAL CLASS: Broad spectrum fluoroquinolone antimicrobial

PROPOSED INDICATION: CILOXAN is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of microorganisms.

RELATED DRUGS/INDs/NDAs:

BACKGROUND INFORMATION: Dr. Lorant Buko of HFD-520 was the original pharmacology/toxicology reviewer for this NDA. Dr. Buko's review was completed in March 1994. Dr. Buko recommended that the drug be approved for human use. Alcon submitted an amendment in June 1997 to address the deficiencies that other disciplines identified during their review of the original submission. On page 3-0252 of the amendment, Alcon refers to toxicology studies conducted with the product packaging. These toxicology studies were inadvertently omitted from the amendment in June 1997. Alcon submitted copies of these reports in September 1997. These studies are addressed in this review.

SUMMARY/REVIEW OF NONCLINICAL STUDIES: The *in vitro* studies discussed below were conducted to determine the biological reactivity of mammalian cell cultures to the tube closure for CILOXAN. The *in vivo* tests were conducted to assess the biological response of animals to the tube closure. The *in vitro* and *in vivo* tests were conducted according to the biological test criteria recommended in USP XII. These studies are generally conducted for drug products that are in contact with plastics and other polymeric materials and are intended to determine the biological reactivity of *in vitro* and *in vivo* systems to elastomeric plastics and other polymeric materials to which patients will be directly or indirectly exposed.

CILOXAN will be packaged in a tamper evident unlined tin tube with a black low density polyethylene closure. The sponsor conducted the USP studies with an item referred to as 'Black LDPE Tube Closures" and with one referred to as "Black LDPE Ointment Tube Closures

the lot numbers for these two items are MD-2017-G and X-0123-G, respectively. According to the chemistry reviewer for this submission, Dr. Rajendra Uppoor, the two terms are used interchangeably.

I. Black LDPE Tube Closure

A. In vitro

- **Study 93G-0739. Agar Diffusion Test with Black LDPE Tube Closures.** (This study was conducted in compliance with GLP at from April 7 to April 9, 1993.)

- **Study 93G-0740. Elution Test with Black LDPE Tube Closures.** (This study was conducted in compliance with GLP at from April 7 to April 9, 1993.)

1. Methods: The methods used in these studies are provided in the table below.

2. Results: Under the conditions of these studies, neither the test article nor its extracts had any effect on the cell cultures. An appropriate response was observed in the cultures exposed to the control articles and their extracts.

B. In vivo

- **Study 93G-0741 and 93G-0742. Acute Systemic Toxicity in Mice and Primary Ocular Irritation in Rabbits of Extracts of Sterilized Black Label LDPE Tube Closures.** (These studies were conducted in compliance with GLP at from April 16 to April 19, 1993.)

1. **Methods:** The acute systemic toxicity and the ocular toxicity tests were conducted with saline and cottonseed oil (CSO) extracts (60 cm^2/20 mL) of the black LDPE tube closures. The extracts were prepared by heating the extractions at 70°C for 24 hours. The treatment protocols used in these two studies are provided in the table below. NaCl (0.9%) and CSO were used as control articles.

Protocols for Studies 93G-0741 and 93G-0742

Test	Species
Systemic toxicity	Mice/Swiss,
Ocular irritation	Rabbit/New Zealand White

2. **Results:** The animals did not exhibit any effects.

II. **Black Label LDPE Ointment Tube Closure**

A. In vitro

- **Study 94G-1474. Agar Diffusion Test with Black LDPE Ointment Tube Closures** (This study was conducted in compliance with GLP at from August 17 to August 19, 1994.)

- **Study 94G-1473. Elution Test with Gamma LDPE Ointment Tube Closures** (This study was conducted in compliance with GLP at from August 17 to August 19, 1994.)

1. Methods: The methods used in these two studies are shown in the table below.

2. Results: Under the conditions of these studies neither the test article nor its extracts had any effect on the cell cultures. An appropriate response was observed in the cultures exposed to the control articles and their extracts.

B. In vivo

- **Study 94G-1472. Acute Systemic Toxicity in Mice with Extracts of Black LDPE Ointment Tube Closures** (This study was conducted in compliance with GLP at from August 17 to August 20, 1994.)

- **Study 94G-1471. Intracutaneous Reactivity Test in Albino Rabbits with Extracts of Black LDPE Ointment Tube Closures** (This study was conducted in compliance with GLP at from August 17 to August 20, 1994.)

1. Methods: The acute systemic toxicity and the intracutaneous toxicity tests were conducted with saline and cottonseed oil (CSO) extracts (60 cm^2/20 mL) of the black LDPE tube closures. The extracts were prepared by heating the extractions at 70°C for 24 hours. The treatment protocols used in these two studies are provided in the table below. NaCl (0.9%) and CSO were used as control articles.

Protocols for Studies 94G-1472 and 94G-1471

Test	Species
Systemic toxicity	Mice/Swiss,
Intracutaneous	Rabbit/New Zealand White

2. Results: The animals did not exhibit any effects.

SUMMARY/CONCLUSION: The *in vitro* and *in vivo* biological reactivity of the tube closures for CILOXAN was assessed according to the recommendations of USP XII. These studies are

generally conducted for drug products that are in contact with plastics and other polymeric materials and are intended to determine the biological reactivity of *in vitro* and *in vivo* systems of materials to which patients will be directly or indirectly exposed. Under the conditions of the studies described above, the tube closure for CILOXAN did not induce reactivity in the *in vitro* or the *in vivo* systems.

3 Nov 97

Andrea B. Weir, Ph.D.
Reviewing Pharmacologist

11/4/97

cc:
Orig NDA 20-369
HFD-550 Division File
HFD-550/CSO/Gorski
HFD-550/Chem/Uppoor
HFD-550/pharm/Weir
HFD-550/TL Pharm/Chen
HFD-550/MO/Chambers

APPEARS THIS WAY ON ORIGINAL

APR 8 1994

Review & Evaluation of Pharmacology and Toxicology Data
Division of Anti-infective Drug Products, HFD-520

NDA 20-369 (000)

Pertinent IND:

Drug Name: Ciprofloxacin HCl Ophthalmic Ointment 0.3% as a Base

Category: Ophthalmic Quinolone Antibacterial

Sponsor: ALCON LABORATORIES,INC.

6201 South Freeway

Forth Worth, Texas 76134-2099

Telephone: 293-0450 TELEX 758320

Number of Volumes: (2)

Date CDER Received: May 24,1993

Date Assigned: 6/13/93

Date Review Started: 1/24/94

Date Review Accepted by Supervisor: March 31, 1994

Review Objectives: To determine the human safety of the subject drug based on animal toxicity studies.

In my review below a telegraphic review of the non-ocular and two ocular studies (One Acute and One Subacute (35 days) are presented.

For the chemical name, structure, composition of the drug product, and other technical data the reader is referred to my original review of

SUMMARY OF NONCLINICAL TOXICOLOGY STUDIES

"Extensive preclinical studies have been conducted/sponsored by Alcon Laboratories,Inc, Miles Laboratories and Bayer AG to substantiate the safety of ciprofloxacin. Summaries from topical ocular studies by Alcon Laboratories,Inc., and summaries from special ophthalmic toxicology studies conducted/sponsored by Bayer AG are presented in this section of the NDA. Summaries from systemic studies conducted/sponsored by Miles Pharmaceuticals and Bayer AG are contained in the Ciprofloxacin Tablets-NDA Supplement.

The summaries and complete reports describing the safety/toxicity of ciprofloxacin concludes:

* Ciprofloxacin does not produce a mutagenic effect in mammalian mutagenicity assay systems.

* Ciprofloxacin has a low acute toxicity potential.

* Oral administration of Ciprofloxacin at doses of 500 mg/kg/day in rats for six months resulted in a low incidence of crystals in the urine sediment. No clinically relevant changes were observed at 20 and 100mg/kg/day.

* Oral administration of Ciprofloxacin at doses of 90mg/kg/day to monkeys for six months resulted in a low incidence of slight to moderate foreign body reaction in the kidneys. No clinically relevant changes were observed at 10 and 30 mg/kg/day.

* Oral administration of Ciprofloxacin to adult dogs at dose

levels of 40-80mg/kg/day for four weeks did not result in any clinically relevant findings. Oral administration of Ciprofloxacin to juvenile dogs at dose levels of 30-100 mg/kg/day for 14 days resulted in dose related degenerative changes in the articular cartilage.

* Oral administration of Ciprofloxacin does not have an adverse effect on the ~~payer~~ pre- and postnatal development on the rat.

* Ciprofloxacin Ophthalmic Solution at concentrations of 0.3%-0.75% has a low ocular irritation potential and does not produce any apparent systemic toxicity including degenerative changes in joints after repeated daily topical ocular administration to young dogs for one month.

* Ciprofloxacin Ophthalmic Ointment at concentrations of 0.3-1.5% has a low ocular irritation potential and produces no apparent systemic toxicity after repeated daily administration to rabbits for one month.

Based on the results of the toxicology/safety studies reported by in the Ciprofloxacin Tablets NDA 19-537, by Alcon laboratories, INC., it was concluded that 0.3%-0.75 Ciprofloxacin Hydro chloride Ophthalmic Ointment does not present an unreasonable ophthalmic or systemic risk to humans and is safe for its intended use in the treatment of ocular in-

fections provided the label indications, precautions and warnings are observed.

REVIEWER'S FINAL REMARKS: Based on the relative systemic non-toxicity of the drug substance and lack of any ocular irritation or toxicity in animal eyes, I feel that the animal safety allows the drug to be approved for human ophthalmic purposes.

Lorant Buko, D.V.M.

cc: Orig IND/NDA
HFD-34
HFD-520 DeSantis
HFD-520/Pharm/LBuko
HFD-520/MO/WChambers
HFD-520/Micro/PDionne
HFD-520/Chem/VShetty

Concurrence Only:
HFD-520/DD/Gavrilovich
HFD-520/Spharm/Reo

3/31/94

4/8/94

APPEARS THIS WAY
ON ORIGINAL