DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED BY FACSIMILE

JUN 12 2000

Scott Krueger
Director, Regulatory Affairs
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

RE: **NDA 19-992 Ciloxan** (ciprofloxacin HCl) 0.3% as base sterile ophthalmic solution
MACMIS ID# 8799

Dear Mr. Krueger:

This letter describes Alcon Laboratories, Inc.'s (Alcon) dissemination of violative promotional materials for Ciloxan. These materials include an unnumbered, two-sided sales aid titled "SOME THINGS AREN'T SO PRETTY IN PINK. CILOXAN wipes out PINK EYE in just 3 days," a brochure (CN00501VS0) with the same title, a brochure (CN99508VS) titled "FIGHT INFECTIONS FAST WITH CILOXAN," and "homemade" promotional materials (Attachment 1) for Ciloxan. The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed these promotional materials and concluded that they are false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, they promote an unapproved dosing regimen, omit important dosing information, and lack fair balance for Ciloxan. Our specific objections follow:

Misleading Claims of Effectiveness

Your materials include claims such as "Ciloxan wipes out pink eye in just 3 days," "Three day action," "QID for 3 days," and "Ciloxan for Infections QID Dosing/3 Days." These claims are misleading because they are inconsistent with the approved product labeling (PI) for Ciloxan and suggest that Ciloxan is only to be used for 3 days for the treatment of bacterial conjunctivitis. However, the PI states that the dosing regimen for bacterial conjunctivitis with Ciloxan is seven days (one or two drops instilled in the conjunctival sac(s) every two hours while awake for two days, and one or two drops every four hours while awake for the next five days). Your materials fail to include this material information. Thus, your suggestion that Ciloxan is to be used for only three days is misleading.

Lack of Fair Balance

Promotional materials are misleading if they fail to present information about the risks associated with the use of the drug with a prominence and readability reasonably

comparable to that of the claims for the drug. The "FIGHT INFECTIONS FAST WITH CILOXAN" brochure is misleading because it lacks fair balance. Specifically, you prominently present safety and efficacy claims on 10 pages of the brochure. These claims are presented in large type size, and are bolded and bulleted for emphasis. In contrast, you present one sentence of risk information, in small type, at the bottom of the last page. In addition, your brochure fails to present important risk information about the use of Ciloxan identified in the Warnings, Precautions, and Adverse Reactions sections of the PI.

Similarly, the "SOME THINGS AREN'T SO PRETTY IN PINK" 2-sided sales aid presents claims about Ciloxan's safety and effectiveness, but fails to present information about the risks associated with the use of the drug with a prominence and readability reasonably comparable to that of the claims for the drug. You present claims about Ciloxan in large type size that is bolded and bulleted for further emphasis. In contrast, you present the risk information in small size, and present the information in running text near the bottom of the rear page.

Your "homemade" pieces for Ciloxan are in violation of the Act because they fail to include any risk information about the product (emphasis added).

Misleading Presentation of *In Vitro* Data

Non-clinical data may not be used in a way that suggests that such data has clinical significance when such clinical significance has not been demonstrated. In the "FIGHT INFECTIONS FAST WITH CILOXAN" brochure and "SOME THINGS AREN'T SO PRETTY IN PINK" sales aid, you present data on *in vitro* kill curves. In the "FIGHT INFECTIONS FAST WITH CILOXAN" brochure, you present the claim that "Ciloxan kills pathogens in minutes." However, there is not necessarily a correlation between *in vitro* activity (MIC_{90} data) and *in vivo* results. Thus, this presentation of non-clinical data is misleading. In the "FIGHT INFECTIONS FAST WITH CILOXAN" brochure, you present *in vitro* data on three pages and qualify the *in vitro* information with the statement, "*In vitro* activity does not necessarily correlate with *in vivo* activity." However, this qualifying information is presented in small type at the bottom of one of three pages and it fails to correct the suggestion that the data presented is clinically significant. Thus, this presentation is also misleading.

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of these violative promotional materials and any other violative

promotional materials for Ciloxan that contain the same or similar claims or presentations.

You should respond to me in writing with your intent to comply with our request by June 26, 2000, providing a list of the promotional materials discontinued, and the date Alcon ceased the dissemination of the promotional materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

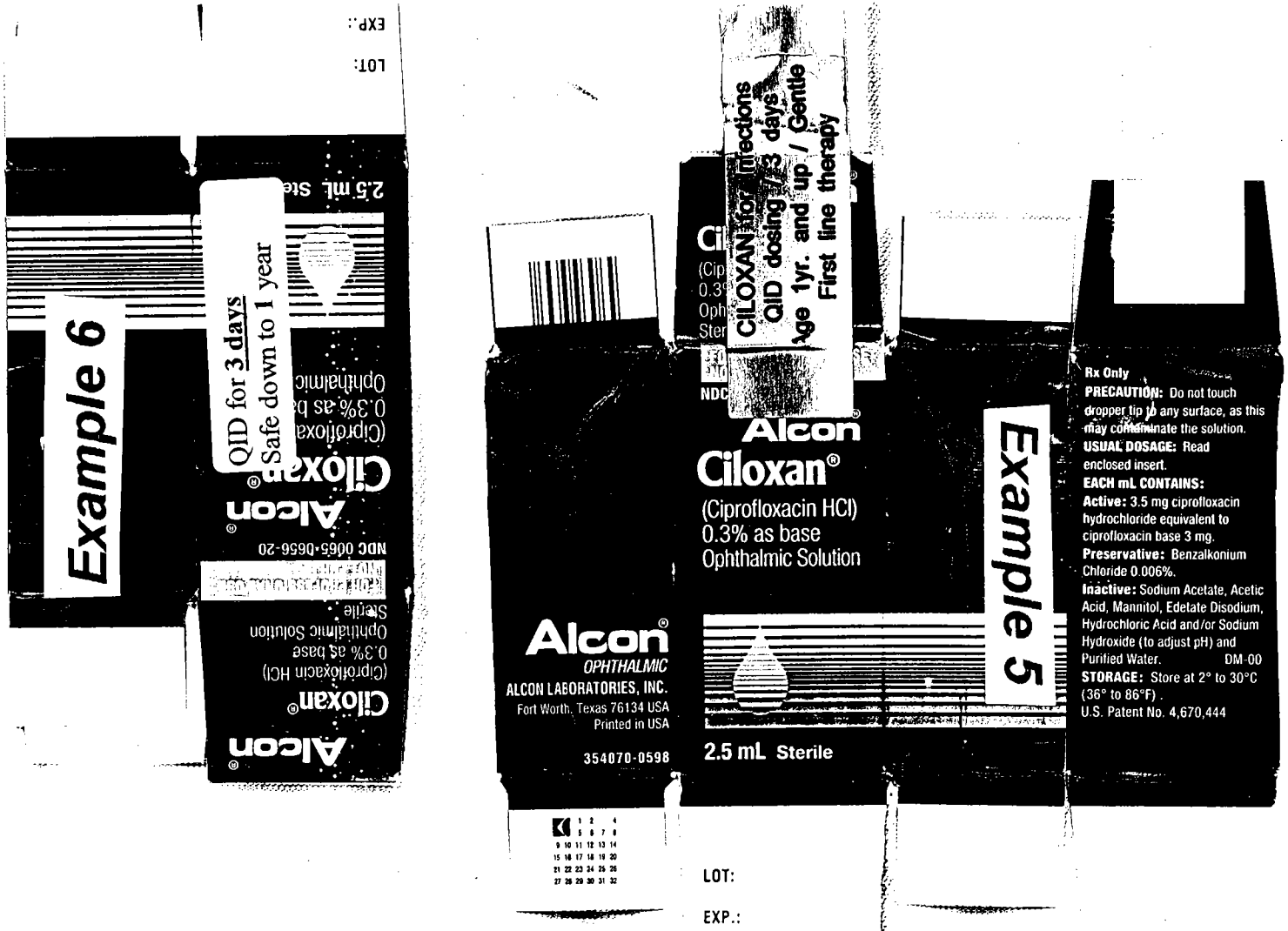
In all future correspondence regarding this matter, please refer to MACMIS # 8799 and NDA 19-992.

Sincerely,

/S/

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

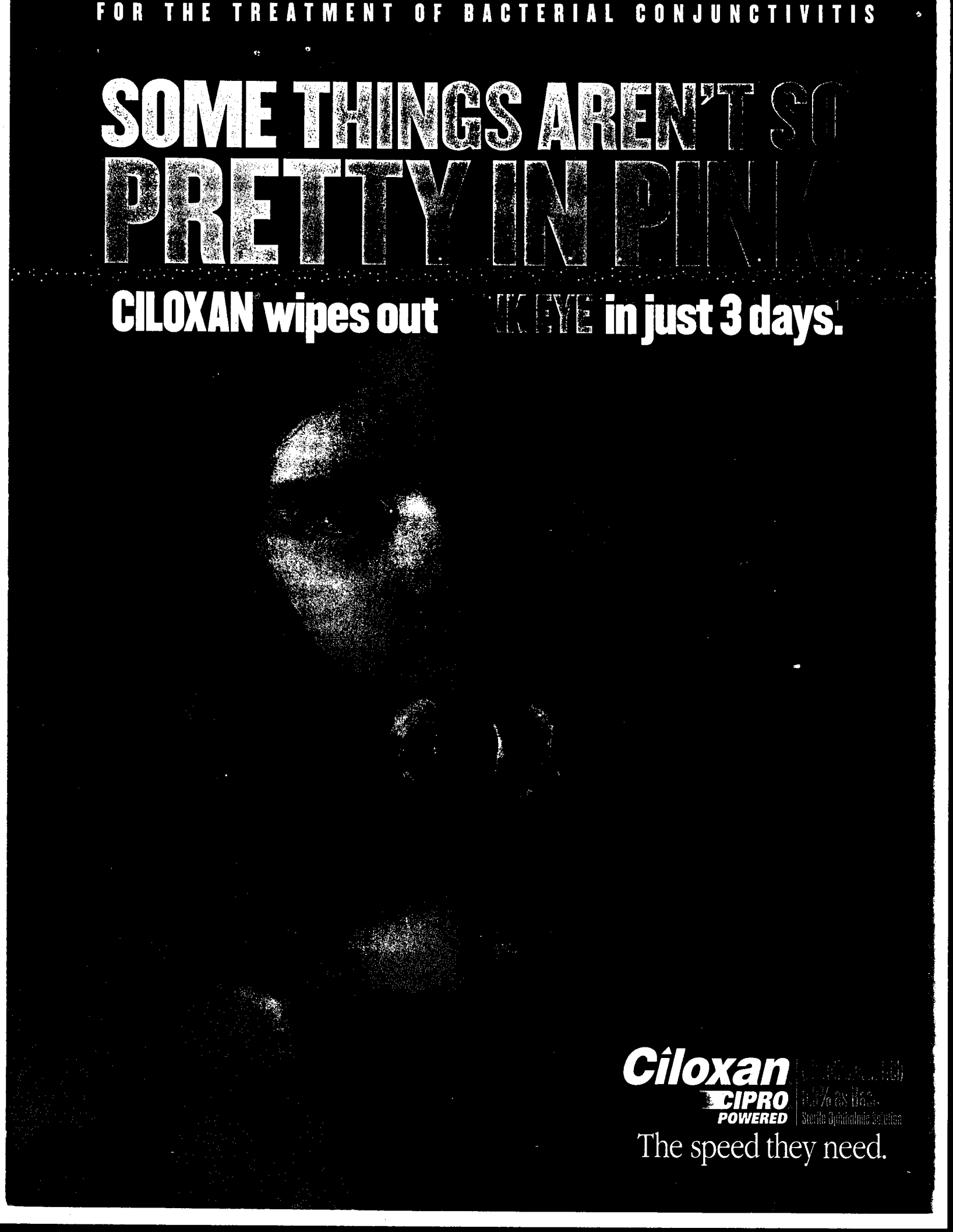
Enclosures: 1


Example 6
QID for 3 days
Safe down to 1 year
Alcon
Ciloxan®
(Ciprofloxacin HCl)
0.3% as base
Ophthalmic Solution
Sterile
NDC 0065-0656-20
LOT:
EXP.:
Example 5
CILOXAN for infections
QID dosing / 3 days
Age 1yr. and up / Gentle
First line therapy
Alcon
Ciloxan®
(Ciprofloxacin HCl)
0.3% as base
Ophthalmic Solution
Alcon
OPHTHALMIC
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA
Printed in USA
354070-0598
2.5 mL Sterile
Rx Only
PRECAUTION: Do not touch dropper tip to any surface, as this may contaminate the solution.
USUAL DOSAGE: Read enclosed insert.
EACH mL CONTAINS:
Active: 3.5 mg ciprofloxacin hydrochloride equivalent to ciprofloxacin base 3 mg.
Preservative: Benzalkonium Chloride 0.006%.
Inactive: Sodium Acetate, Acetic Acid, Mannitol, Edetate Disodium, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water.
DM-00
STORAGE: Store at 2° to 30°C (36° to 86°F).
U.S. Patent No. 4,670,444
LOT:
EXP.:

FOR THE TREATMENT OF BACTERIAL CONJUNCTIVITIS

SOME THINGS AREN'T SO PRETTY IN PINK.

CILOXAN® wipes out PINK EYE in just 3 days.[1]



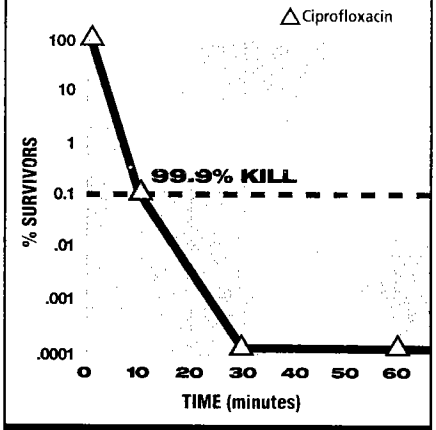
Ciloxan®
CIPRO® POWERED
0.3% ciprofloxacin ophthalmic solution
Sterile Ophthalmic Solution

The speed they need.

CILOXAN® FIGHTS INFECTIONS FAST

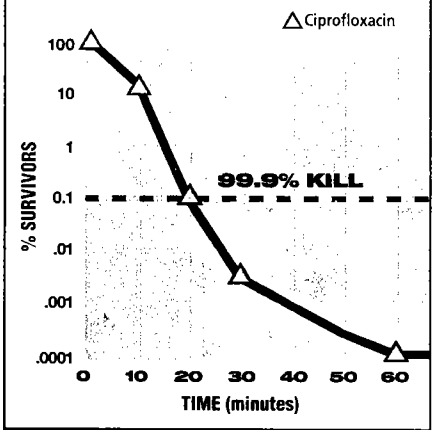
In Vitro KILL CURVES[2]

Streptococcus pneumoniae



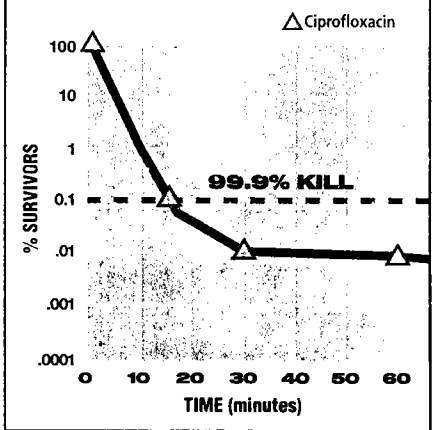
Ciprofloxacin: Kill reached at 10 minutes

Haemophilus influenzae



Ciprofloxacin: Kill reached at 20 minutes

Staphylococcus aureus



Ciprofloxacin: Kill reached at 15 minutes

KNOCKS OUT THE TOUGHEST PATHOGENS

CIPROFLOXACIN MIC_{90} VALUES FOR SERIOUS BACTERIAL CONJUNCTIVITIS PATHOGENS[2]

ISOLATE	MIC_{90} (µg/mL)	Susceptibility Rates
Strep. pneumoniae	1.0	97%
H. influenzae	0.008	100%
Staph. aureus	0.25	99%
*Staph. epi (MS)**	4.0	96%
P. aeruginosa	0.25	95%
S. marcescens	0.12	100%

*MS (methicillin-susceptible).

In vitro susceptibility testing of 1,204 ocular isolates. Performed by Clyde Thornsberry, PhD (Previous Director of Antibiotics for 23 years at the Centers for Disease Control, Atlanta, GA), MRL Pharmaceutical Services, Franklin, Tennessee. MIC_{90} values ratified by the National Committee for Clinical and Laboratories Standards.

- **Fast eradication of the toughest ocular pathogens**
- **Unsurpassed eradication of the most prevalent causative bacterial conjunctivitis pathogens, *H. flu* and *Strep. pneumo*[3]**
- **Established pediatric safety:**
  - *Solution 1 year and older*
  - *Ointment 2 years and older*
- **No.1 prescribed ocular fluoroquinolone[4]**

References:
1. Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *Am J Ophthalmol.* 1991;112(suppl):29S-33S.
2. Data on file, Alcon Laboratories, Inc.
3. Weiss A, Brinser J, Nazar-Stewart V. Acute conjunctivitis in childhood. *J Pediatr.* 1993;122:10-14.
4. Source™ Prescription Audit (SPA), December 1998 – November 1999. Scott-Levin, Inc.

CILOXAN® should be discontinued at the first appearance of a skin rash or any other signs of hypersensitivity reaction. *In vitro* data are not always indicative of clinical success or microbiological eradication in a clinical setting. As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms including fungi.

Ciloxan® (ciprofloxacin HCl) 0.3% as Base Sterile Ophthalmic Solution

The speed they need.

Alcon® PHARMACEUTICALS
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134
www.alconlabs.com

Treating pink eye is easy with CILOXAN®.

How to use CILOXAN® Solution

❶ Have your child lie flat on his or her back, head tilted upwards.

❷ With clean hands, gently pull down the lower lid of the infected eye(s) with your index finger.

❸ Hold bottle directly above the eye. Don't touch the tip of the container of CILOXAN® to the infected eye or to any other surface, as this may lead to contamination of the other eye and/or the medication in the container. Then squeeze a drop of CILOXAN® Solution into the eye. Administer only as many drops as prescribed for each dosage. Don't make up for missed doses.

If additional eye drop medications have been prescribed, allow at least 10 minutes between doses. This will ensure maximum effectiveness of all drops.

Alcon® PHARMACEUTICALS

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134
www.alconlabs.com

CIPRO® is a registered trademark of Bayer AG.

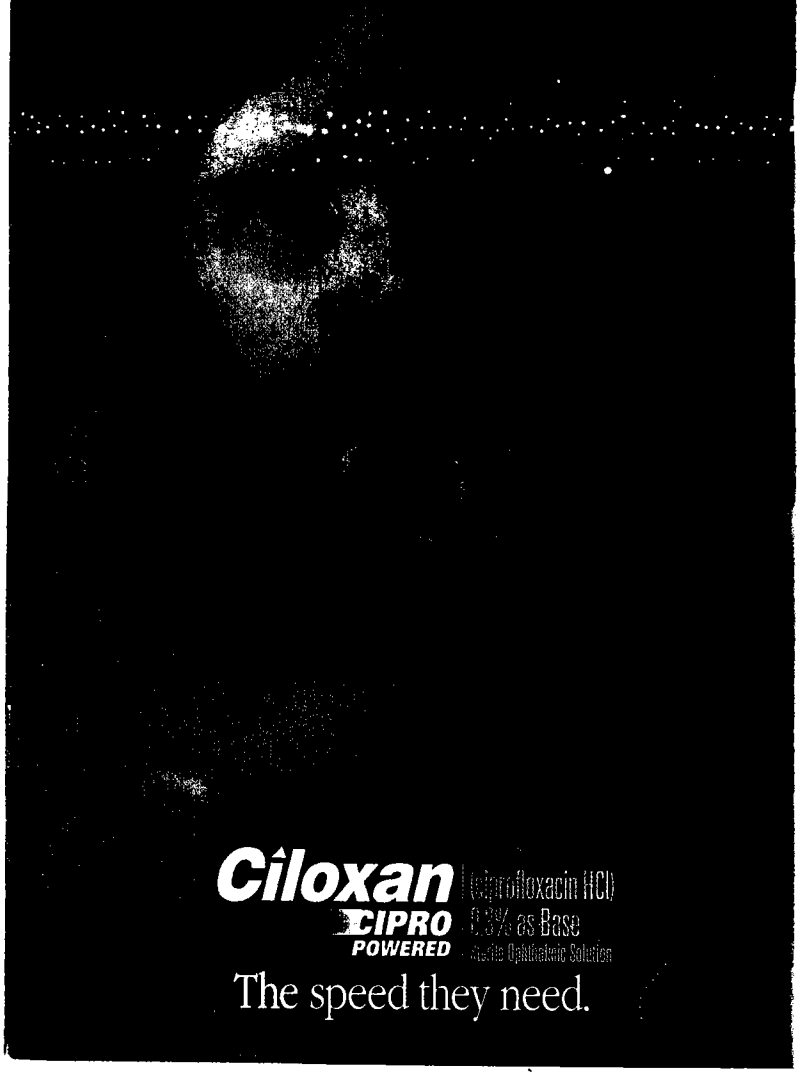
References:
1. Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *Am J Ophthalmol.* 1991;112(suppl):29S-33S.
2. Source™ Prescription Audit (SPA). December 1998 – November 1999. Scott-Levin, Inc.

 1/00 CN00501VS Printed in U.S.A.

A GUIDE TO PINK EYE FOR PARENTS AND PATIENTS

SOME THINGS AREN'T SO PRETTY IN PINK.

CILOXAN® wipes out PINK EYE in just 3 days.[1]



Ciloxan Ciprofloxacin HCl 0.3% as Base Sterile Ophthalmic Solution
CIPRO POWERED

The speed they need.

A GUIDE TO PINK EYE FOR PARENTS AND PATIENTS

What is pink eye?

Pink eye is another name for *infectious conjunctivitis* of bacterial or viral origin, a common eye infection that can easily be transferred from one person to another.

How does pink eye develop and spread?

Pink eye occurs when bacteria or viruses that infect the eye cause an inflammation of the *conjunctiva*, the transparent membrane that covers the eye. Eyes then become red and irritated and may produce a burning or itchy feeling as well as a sticky mucous discharge.

When infected patients rub their eyes, they are unknowingly contaminating their fingers and hands. By then touching another person or a shared article such as a towel, blanket, or makeup, they can easily pass the infection along.

Is pink eye serious?

Pink eye is generally not a serious condition. It is, however, highly contagious and may require your child to stay home from school until he or she is no longer at risk of spreading the infection.

Why did my child's doctor prescribe CILOXAN®?

When pink eye strikes, you want a therapy that works fast to clear up the bacterial infection and return your child to school quickly. That's why your child's doctor prescribed CILOXAN®, which is the No. 1 prescribed eye drop in its class.[2]

CILOXAN® works fast to fight the tough bacteria that cause pink eye. In most cases, children treated with CILOXAN® who are symptom-free can return to school in as soon as 3 days. And CILOXAN® Solution has been proven safe for children 1 year of age and older (CILOXAN® Ointment: 2 years of age and older).

As with any prescription medication, be sure to follow your doctor's instructions regarding use of CILOXAN®.

What can I do to prevent the spread of pink eye?

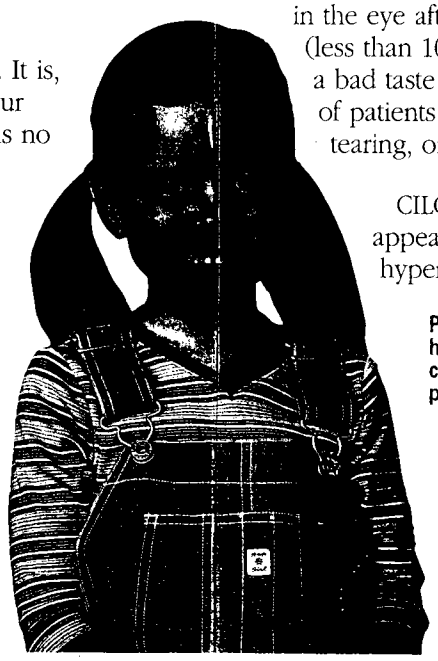
Wash any articles that may have touched the infected eyes, including clothing, blankets, and towels. Also, instruct your child to practice the following smart hygiene habits:

- *Wash hands thoroughly and often throughout the day*
- *Don't touch or rub the eyes*
- *Don't share eyewear, towels, blankets, makeup, or similar items with other children*

Are there any side effects to CILOXAN®?

Some patients may experience burning or discomfort in the eye after instillation. A small percentage of patients (less than 10%) may experience eyelid crusting, itching, or a bad taste upon instillation of the eye drops. Less than 1% of patients report blurred vision, dry eye, allergic reactions, tearing, or similar irritations.

CILOXAN® should be discontinued at the first appearance of a skin rash or any other signs of hypersensitivity reaction.



Please refer to the back page for detailed instructions on how to use CILOXAN®. For any questions or concerns not covered in this brochure, ask your doctor or refer to the product's prescribing information.

Ciloxan® (ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution

The speed they need.

Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

- No. 1 prescribed ocular fluoroquinolone among primary care physicians[3]
- In just 3 days, CILOXAN® Solution eradicated or reduced approximately 94% of causative pathogens[1]
- Active against 48 different ocular pathogens
- Established pediatric safety:
  —Solution: 1 year and older
  —Ointment: 2 years and older

FIGHT INFECTIONS FAST

Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment
THE SPEED THEY NEED

Alcon®
PHARMACEUTICALS

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134
www.alconlabs.com

CILOXAN® should be discontinued at the first appearance of a skin rash or any other signs of hypersensitivity reaction.

Please see full prescribing information on pages 10-15.

7/99 CN99508VS Printed in U.S.A.

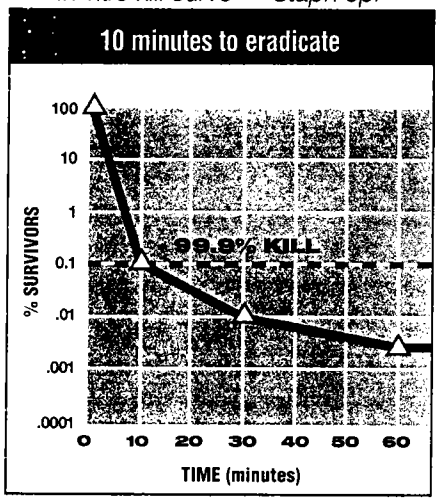
FIGHT INFECTIONS FAST WITH CILOXAN®

CILOXAN® KILLS PATHOGENS IN MINUTES

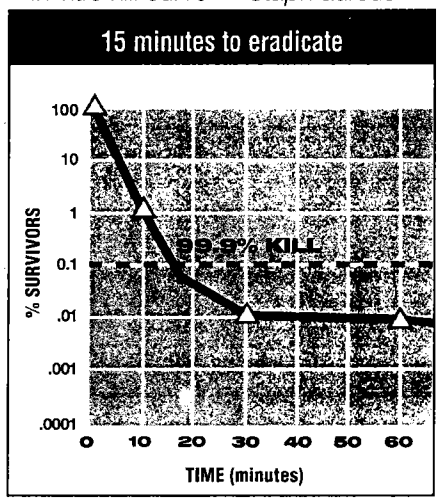
Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

THE SPEED THEY NEED

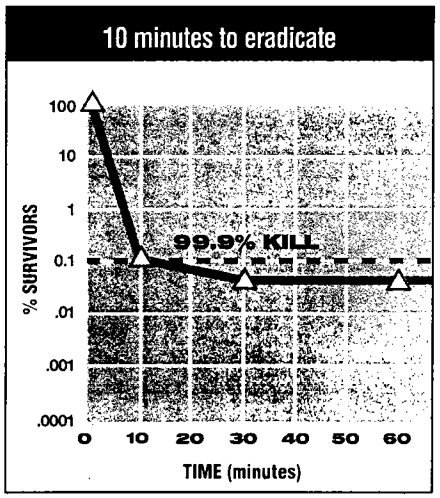
In vitro kill curve — Staph epi[1]



In vitro kill curve — Staph aureus[1]



In vitro kill curve — Pseudomonas a[1]



Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

THREE-DAY ACTION

In Just 3 Days:

- CILOXAN® Solution eradicated or reduced approximately 94% of causative pathogens[1]
- Physicians determined that 50% of patients with bacterial conjunctivitis were symptom free[2]

Active Against 48 Different Ocular Pathogens *In Vitro**

Including...

- *Haemophilus influenzae*
- *Staphylococcus epidermidis*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

**In vitro* activity does not necessarily correlate with *in vivo* activity.

Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

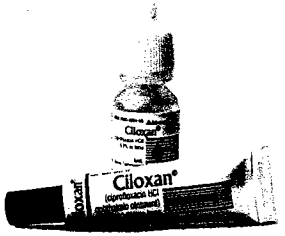
Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

THE SPEED THEY NEED

Established Pediatric Safety:

CILOXAN® Solution
— 1 year and older

CILOXAN® Ointment
— 2 years and older



Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

THE SPEED THEY NEED

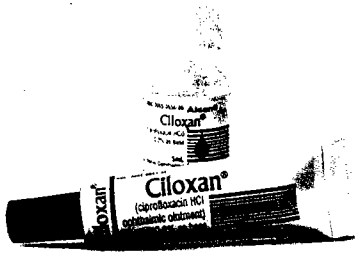
THE NO.1 PRESCRIBED OCULAR FLUOROQUINOLONE AMONG PRIMARY CARE PHYSICIANS[3]

Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment
THE SPEED THEY NEED

Ciloxan®
(ciprofloxacin HCl) 0.3% as Base
Sterile Ophthalmic Solution & Ointment

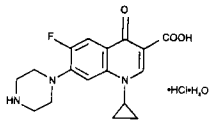
Now Available in Ointment Form

Ointment and solution provide convenient treatment options for 24-hour coverage



CILOXAN®
(Ciprofloxacin HCl)
0.3% as base Sterile Ophthalmic Solution and Ointment

DESCRIPTION: CILOXAN® (Ciprofloxacin HCl) Ophthalmic Solution and Ointment are synthetic, sterile, multiple dose, antimicrobials for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. It is a faint to light yellow crystalline powder with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is shown at right:



Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-position.

Each mL of CILOXAN Ophthalmic Solution contains: **Active:** Ciprofloxacin HCl 3.5 mg equivalent to 3 mg base. **Preservative:** Benzalkonium Chloride 0.006%. **Inactive:** Sodium Acetate, Acetic Acid, Mannitol 4.6%, Edetate Disodium 0.05%, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water. The pH is approximately 4.5 and the osmolality is approximately 300 mOsm.

Each gram of CILOXAN Ophthalmic Ointment contains: **Active:** Ciprofloxacin HCl 3.33 mg equivalent to 3 mg base. **Inactives:** Mineral Oil, White Petrolatum.

DM-00

CLINICAL PHARMACOLOGY:

Systemic Absorption: A systemic absorption study was performed in which CILOXAN Ophthalmic Solution was administered in each eye every two hours while awake for two days followed by every four hours while awake for an additional 5 days. The maximum reported plasma concentration of ciprofloxacin was less than 5 ng/mL. The mean concentration was usually less than 2.5 ng/mL. Ointment mean concentration levels have not been determined but are expected to be similar.

Microbiology: Ciprofloxacin has in vitro activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase which is needed for the synthesis of bacterial DNA.

Ciprofloxacin has been shown to be active against most strains of the following organisms both in vitro and in clinical infections. (See INDICATIONS AND USAGE section).

Gram-Positive:
Staphylococcus aureus (including methicillin-susceptible and methicillin-resistant strains)
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Viridans Group)

Gram-Negative:
Haemophilus influenzae
Pseudomonas aeruginosa
Serratia marcescens

Ciprofloxacin has been shown to be active in vitro against most strains of the following organisms, however, the clinical significance of these data is unknown:

Gram-Positive:
Bacillus species
Corynebacterium species
Enterococcus faecalis (Many strains are only moderately susceptible)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus saprophyticus
Streptococcus pyogenes

Gram-Negative:
Acinetobacter calcoaceticus subsp. anitratus
Aeromonas caviae
Aeromonas hydrophila
Brucella melitensis
Campylobacter coli
Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus ducreyi
Haemophilus parainfluenzae
Klebsiella pneumoniae
Klebsiella oxytoca
Legionella pneumophila
Moraxella (Branhamella) catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Neisseria meningitidis
Pasteurella multocida
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella enteritidis
Salmonella typhi
Shigella sonnei
Shigella flexneri
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Other Organisms: *Chlamydia trachomatis* (only moderately susceptible) and *Mycobacterium tuberculosis* (only moderately susceptible).

Most strains of *Pseudomonas cepacia* and *Burkholderia cepacia* and some strains of *Pseudomonas maltophilia* and *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-step mutation).

Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. Organisms resistant to ciprofloxacin may be susceptible to beta-lactams or aminoglycosides.

Clinical Studies:

Following therapy with CILOXAN Ophthalmic Solution, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization occurred in about 92% of the ulcers.

In 3 and 7 day multicenter clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70-80% had all causative pathogens eradicated by the end of treatment. Following therapy with CILOXAN Ointment 75% of the patients with signs and symptoms of bacterial conjunctivitis and positive conjunctival cultures were clinically cured and approximately 80% had presumed pathogens eradicated by the end of treatment (day 7).

INDICATIONS AND USAGE: CILOXAN Ophthalmic Solution and CILOXAN Ophthalmic Ointment are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Conjunctivitis – Solution and Ointment:
Haemophilus influenzae
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Viridans Group)

Corneal Ulcers – Solution only:
Pseudomonas aeruginosa
*Serratia marcescens**
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus (Viridans Group)*

*Efficacy for these organisms was studied in fewer than 10 infections.

CONTRAINDICATIONS: A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS: NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

PRECAUTIONS: General: As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction. Ophthalmic ointments may retard corneal healing and cause visual blurring. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24-72 hours), in five patients, resolution was noted in 10-13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations, 18-44 days after onset of the event, complete resolution of the precipitate was noted. In three patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (SEE ADVERSE REACTIONS).

Information for patients: Do not touch tip to any surface, as this may contaminate the product.

Drug Interactions: Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight in vitro mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three in vivo test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to two years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Pregnancy – Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women. CILOXAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topically applied ciprofloxacin is excreted in human milk; however, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when CILOXAN is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 1 year (solution) and 2 years (ointment) have not been established.

Although ciprofloxacin and other quinolones cause arthropathy in immature Beagle dogs after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

ADVERSE REACTIONS: The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% (solution) and 13% (ointment) of patients (SEE PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision, blurred vision, dry eye, epitheliopathy, eye pain, irritation and dermatitis.

OVERDOSAGE: A topical overdose of CILOXAN Ophthalmic Solution may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION:

Bacterial Conjunctivitis: *Solution:* The recommended dosage regimen for the treatment of bacterial conjunctivitis is one or two drops of CILOXAN Ophthalmic Solution instilled into the conjunctival sac(s) every two hours while awake for two days and one or two drops every four hours while awake for the next five days. *Ointment:* Apply a 1/2" ribbon into the conjunctival sac three times a day on the first two days, then apply a 1/2" ribbon two times a day for the next five days.

Corneal Ulcers: The recommended dosage regimen for the treatment of corneal ulcers is two drops of the *Solution* into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. On the third through the fourteenth day, place two drops in the affected eye every four hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.

HOW SUPPLIED: As a sterile ophthalmic solution in 2.5 mL (**NDC** 0065-0656-25) and 5 mL (**NDC** 0065-0656-05) in plastic DROP-TAINER® dispensers. Sterile ophthalmic ointment in 3.5 g ophthalmic tube (**NDC** 0065-0654-35).

STORAGE: Solution: Store at 2° to 30°C (36° to 86°F). Protect from light.
Ointment: Store at 2° C to 25° C (36° F to 77° F)

ANIMAL PHARMACOLOGY: Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one-month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.

CAUTION: Rx Only

U.S. Patent No. 4,670,444 Revised: April 1998

References:
1. Data on file, Alcon Laboratories, Inc.
2. Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *Am J Ophthalmol.* 1991;112(suppl):29S-33S.
3. *Source™ Prescription Audit (SPA),* January 1998-December 1998, PMSI Scott-Levin, Inc.

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