9011208

MERCK & CO., INC.
West Point, PA 19486, USA

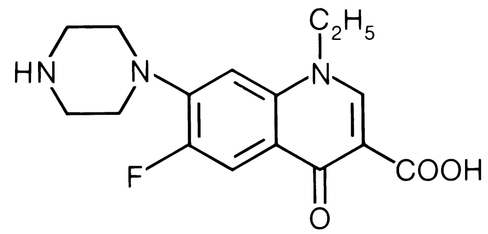
STERILE OPHTHALMIC SOLUTION

CHIBROXIN®

(NORFLOXACIN OPHTHALMIC SOLUTION)

DESCRIPTION

CHIBROXIN* (norfloxacin ophthalmic solution) is a synthetic broad-spectrum antibacterial agent supplied as a sterile isotonic solution for topical ophthalmic use. Norfloxacin, a fluoroquinolone, is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{16}H_{18}FN_3O_3$ and the structural formula is:



Norfloxacin is a white to pale yellow crystalline powder with a molecular weight of 319.34 and a melting point of about 221°C. It is freely soluble in glacial acetic acid and very slightly soluble in ethanol, methanol and water.

CHIBROXIN Ophthalmic Solution 0.3% is supplied as a sterile isotonic solution. Each mL contains 3 mg norfloxacin. Inactive ingredients: disodium edetate, sodium acetate, sodium chloride, hydrochloric acid (to adjust pH) and water for injection. Benzalkonium chloride 0.0025% is added as preservative. The pH of CHIBROXIN is approximately 5.2 and the osmolarity is approximately 285 mOsmol/liter.

Norfloxacin, a fluoroquinolone, differs from quinolones by having a fluorine atom at the 6 position and a piperazine moiety at the 7 position.

CLINICAL PHARMACOLOGY

Microbiology

Norfloxacin has *in vitro* activity against a broad spectrum of gram-positive and gram-negative aerobic bacteria. The fluorine atom at the 6 position provides increased potency against gram-negative organisms and the piperazine moiety at the 7 position is responsible for anti-pseudomonal activity.

Norfloxacin inhibits bacterial deoxyribonucleic acid synthesis and is bactericidal. At the molecular level three specific events are attributed to CHIBROXIN in *E. coli* cells:

1) inhibition of the ATP-dependent DNA supercoiling reaction catalyzed by DNA gyrase;
2) inhibition of the relaxation of supercoiled DNA;
3) promotion of double-stranded DNA breakage.

There is generally no cross-resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin generally demonstrates activity against indicated organisms resistant to some other antimicrobial agents. When such cross-resistance does occur, it is probably due to decreased entry of the drugs into the bacterial cells. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin.

Norfloxacin has been shown to be active against most strains of the following organisms both *in vitro* and clinically in ophthalmic infections (see INDICATIONS AND USAGE):

Gram-positive bacteria including:
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus warnerii
Streptococcus pneumoniae

Gram-negative bacteria including:
Acinetobacter calcoaceticus
Aeromonas hydrophila
Haemophilus influenzae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Norfloxacin has been shown to be active *in vitro* against most strains of the following organisms; however, *the clinical significance of these data in ophthalmic infections is unknown.*

Gram-positive bacteria:
Bacillus cereus
Enterococcus faecalis (formerly *Streptococcus faecalis*)
Staphylococcus saprophyticus

Gram-negative bacteria:
Citrobacter diversus
Citrobacter freundii

Edwardsiella tarda
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Hafnia alvei
Haemophilus aegyptius (Koch-Weeks bacillus)
Klebsiella oxytoca
Klebsiella pneumoniae
Klebsiella rhinoscleromatis
Morganella morganii
Neisseria gonorrhoeae
Proteus vulgaris
Providencia alcalifaciens
Providencia rettgeri
Providencia stuartii
Salmonella typhi
Vibrio cholerae
Vibrio parahemolyticus
Yersinia enterocolitica

Other:
Ureaplasma urealyticum

Norfloxacin is not active against obligate anaerobes.

Clinical Studies

Clinical studies were conducted comparing CHIBROXIN Ophthalmic Solution (n=152) with ophthalmic solutions of tobramycin, gentamicin, and chloramphenicol (n=158) in patients with conjunctivitis and positive bacterial cultures. After seven days of therapy with CHIBROXIN Ophthalmic Solution, 72 percent of patients were clinically cured. Of those cured, 85 percent had all their pathogens eradicated. Eradication was also achieved in 62 percent (23/37) of patients whose clinical outcome was not completely cured by day seven. These results were similar among all treatment groups.

Another clinical study compared CHIBROXIN Ophthalmic Solution with placebo in patients with conjunctivitis and positive bacterial cultures. Placebo in this study was the liquid vehicle for CHIBROXIN Ophthalmic Solution and contained the preservative. After five days of therapy, 64 percent (36/56) of patients on CHIBROXIN Ophthalmic Solution were clinically cured compared to 50 percent (23/46) of patients receiving placebo. Of those cured, 78 percent had all their pathogens eradicated. Eradication was also achieved in 50 percent (10/20) of patients whose clinical outcome was not completely cured. The response to CHIBROXIN Ophthalmic Solution was statistically significantly better than the response to placebo.

INDICATIONS AND USAGE

CHIBROXIN Ophthalmic Solution is indicated for the treatment of conjunctivitis when caused by susceptible strains of the following bacteria:

*Acinetobacter calcoaceticus***
*Aeromonas hydrophila***
Haemophilus influenzae
*Proteus mirabilis***
*Pseudomonas aeruginosa***
*Serratia marcescens***
Staphylococcus aureus
Staphylococcus epidermidis
*Staphylococcus warnerii***
Streptococcus pneumoniae

Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of CHIBROXIN Ophthalmic Solution.

CONTRAINDICATIONS

CHIBROXIN Ophthalmic Solution is contraindicated in patients with a history of hypersensitivity to norfloxacin, or the other members of the quinolone group of antibacterial agents or any other component of this medication.

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactoid or 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 anaphylactoid or anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids and airway management, including intubation, should be administered as indicated.

PRECAUTIONS

General

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate measures 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.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. (See PRECAUTIONS, *Information for Patients.*)

**Efficacy for this organism was studied in fewer than 10 infections.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular preparations, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated preparations (see PRECAUTIONS, *General*). If redness, irritation, swelling or pain persists or becomes aggravated, the patient should be advised to consult a physician.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Patients should be advised that norfloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.

Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Drug Interactions

Specific drug interaction studies have not been conducted with norfloxacin ophthalmic solution. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, and enhance the effects of the oral anticoagulant warfarin and its derivatives. Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with norfloxacin. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No increase in neoplastic changes was observed with norfloxacin as compared to controls in a study in rats, lasting up to 96 weeks at doses eight to nine times the usual human oral dose***.

Norfloxacin was tested for mutagenic activity in a number of *in vivo* and *in vitro* tests. Norfloxacin had no mutagenic effect in the dominant lethal test in mice and did not cause chromosomal aberrations in hamsters or rats at doses 30 to 60 times the usual oral dose***. Norfloxacin had no mutagenic activity *in vitro* in the Ames microbial mutagen test, Chinese hamster fibroblasts and V-79 mammalian cell assay. Although norfloxacin was weakly positive in the Rec-assay for DNA repair, all other mutagenic assays were negative including a more sensitive test (V-79).

Norfloxacin did not adversely affect the fertility of male and female mice at oral doses up to 33 times the usual human oral dose***.

Pregnancy

Teratogenic Effects — Pregnancy Category C. Norfloxacin has been shown to produce embryonic loss in monkeys when given in doses 10 times the maximum human oral dose*** (400 mg b.i.d.), with peak plasma levels that are two to three times those obtained in humans. There has been no evidence of a teratogenic effect in any of the animal species tested (rat, rabbit, mouse, monkey) at 6 to 50 times the human oral dose. There are no adequate and well-controlled studies in pregnant women. CHIBROXIN Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether norfloxacin is excreted in human milk following ocular administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from norfloxacin, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see ANIMAL PHARMACOLOGY).

Pediatric Use

Safety and effectiveness in infants below the age of one year have not been established.

Although quinolones including norfloxacin have been shown to cause arthropathy in immature animals after oral administration, topical ocular administration of other quinolones to immature animals has not shown any arthropathy and there is no evidence that the ophthalmic dosage form of those quinolones has any effects on the weight-bearing joints.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and young patients.

ADVERSE REACTIONS

In clinical trials, the most frequently reported drug-related adverse reaction was local burning or discomfort. Other drug-related adverse reactions were conjunctival hyperemia, chemosis, corneal deposits, photophobia and a bitter taste following instillation.

DOSAGE AND ADMINISTRATION

The recommended dose in adults and pediatric patients (one year and older) is one or two drops of CHIBROXIN Ophthalmic Solution applied topically to the affected eye(s) four times daily for up to seven days. Depending on the severity of the infection, the dosage for the first day of therapy may be one or two drops every two hours during the waking hours.

***All factors are based on a standard patient weight of 50 kg. The usual oral dose of norfloxacin is 800 mg daily. One drop of CHIBROXIN Ophthalmic Solution 0.3% contains about 1/6,666 of this dose (0.12 mg).

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HOW SUPPLIED

CHIBROXIN Ophthalmic Solution is a clear, colorless to light yellow solution.

No. 3526 — CHIBROXIN Ophthalmic Solution 0.3% is supplied in a white, opaque, plastic OCUMETER* ophthalmic dispenser with a controlled drop tip as follows:

NDC 0006-3526-03, 5 mL.

Storage

Store CHIBROXIN Ophthalmic Solution at room temperature, 15-30°C (59-86°F). Protect from light.

ANIMAL PHARMACOLOGY

The oral administration of single doses of norfloxacin, six times the recommended human oral dose***, caused lameness in immature dogs. Histologic examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs also produced erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

ADDITIONAL CAUTIONARY INFORMATION

Norfloxacin is available as an oral dosage form in addition to the ophthalmic dosage form. The following adverse effects, while they have not been reported with the ophthalmic dosage form, have been reported with the oral dosage form. However, it should be noted that the usual dosage of oral norfloxacin (800 mg/day) contains 6,666 times the amount in one drop of CHIBROXIN Ophthalmic Solution 0.3% (0.12 mg).

Convulsions have been reported in patients receiving oral norfloxacin. Convulsions, increased intracranial pressure, and toxic psychoses have been reported with other drugs in this class. Orally administered quinolones may also cause central nervous system (CNS) stimulation which may lead to tremors, restlessness, lightheadedness, confusion and hallucinations. If these reactions occur in patients receiving norfloxacin, the drug should be discontinued and appropriate measures instituted.

The effects of norfloxacin on brain function or on the electrical activity of the brain have not been tested. Therefore, as with the oral formulation, norfloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis, epilepsy, and other factors which predispose to seizures.

The following adverse effects have been reported with Tablets NOROXIN* (norfloxacin tablets).

Hypersensitivity Reactions: Hypersensitivity reactions including anaphylactoid reactions, angioedema, arthralgia, arthritis, dyspnea, myalgia, urticaria, vasculitis; *Gastrointestinal:* Hepatitis, jaundice, including cholestatic jaundice, pancreatitis, pseudomembranous colitis; *Hematologic:* Hemolytic anemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency, leukopenia, neutropenia, thrombocytopenia; *Musculoskeletal:* Possible exacerbation of myasthenia gravis, tendinitis, tendon rupture; *Nervous System/Psychiatric:* Ataxia, CNS effects characterized as generalized seizures and myoclonus; Guillain-Barré syndrome, paresthesia, peripheral neuropathy, psychic disturbances including confusion, depression, psychotic reactions; *Renal:* Interstitial nephritis, renal failure; *Skin:* Erythema multiforme and Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity, rash, toxic epidermal necrolysis; *Special Senses:* Diplopia, tinnitus, transient hearing loss.

Abnormal laboratory values observed with oral norfloxacin included elevation of ALT (SGPT) and AST (SGOT), alkaline phosphatase, BUN, serum creatinine, and LDH.

Please consult the package circular for Tablets NOROXIN (norfloxacin tablets) for additional information concerning these and other adverse effects and other cautionary information.

Dist by:
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