

PRODUCT MONOGRAPH

CIPRODEX[®]

Ciprofloxacin Hydrochloride & Dexamethasone
Otic Suspension (0.3% ciprofloxacin / 0.1% w/v)

Antibacterial - Corticosteroid (Otic)

Alcon Canada Inc
2665 Meadowpine Blvd
Mississauga, Ontario
L5N 8C7

Date of Preparation:
May 6, 2004

Control: 081075

PRODUCT MONOGRAPH

CIPRODEX[®]

Ciprofloxacin Hydrochloride & Dexamethasone
Otic Suspension (0.3% ciprofloxacin / 0.1% w/v)

Antibacterial - Corticosteroid (Otic)

ACTIONS & CLINICAL PHARMACOLOGY

Ciprofloxacin, a fluoroquinolone antibiotic, has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzyme, DNA gyrase, which is required for the synthesis of bacterial DNA.

Dexamethasone, a potent corticosteroid, has been shown to aid in the resolution of inflammation.

Clinical Pharmacology: Following a single bilateral 4-drop topical otic dose of CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension to pediatric patients following tympanostomy tube insertion, measurable plasma concentrations of ciprofloxacin and dexamethasone were observed up to 6 hours. In 25 patients, the mean (\pm SD) peak plasma concentrations of ciprofloxacin and dexamethasone were 1.14 ± 0.98 ng/mL and 0.86 ± 1.19 ng/mL, respectively, and were observed typically within 15 minutes to 2 hours post-dose. For ciprofloxacin, these levels were approximately 650-fold lower than levels achieved with an oral dose of 250 to 1000 mg.¹ This bilateral exposure resulted in a peak dexamethasone concentration approximately 9-fold lower than reported by following an oral 0.5mg dose.² Estimates of half-life averaged 3.1 hours for ciprofloxacin and 4.5 hours for dexamethasone. Both values are similar to those reported after oral doses in adults.^{1,3} While systemic exposure was assessed with bilateral administration, most AOMT patients in the clinical trials for this product had unilateral infections (77%).

INDICATIONS AND USAGE

CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension is indicated for the treatment of infections caused by most strains of the designated microorganisms in the specific conditions listed below:

Acute Otitis Media with Otorrhea through tympanostomy tubes in pediatric patients, age 6 months and older, due to:

Aerobic, Gram-Positive:

Streptococcus pneumoniae

Staphylococcus aureus

Aerobic, Gram-Negative:

Haemophilus influenzae

Moraxella catarrhalis

Pseudomonas aeruginosa

Acute Otitis Externa in pediatric, adult and elderly patients, age 1 year and older, due to:

Aerobic, Gram-Positive:

Staphylococcus aureus

Aerobic, Gram-Negative:

Pseudomonas aeruginosa

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin, to other quinolones including nalidixic acid, or to any of the components in this medication. Use of this product is contraindicated in viral infections of the external canal including herpes simplex infections.

WARNINGS

FOR TOPICAL OTIC USE ONLY (This product is not approved for ophthalmic use).

NOT FOR INJECTION.

CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Serious acute hypersensitivity reactions may require immediate emergency treatment.

PRECAUTIONS

General: As with other antibacterial preparations, use of this product may result in overgrowth of nonsusceptible organisms, including yeast and fungi. If the infection is not improved after one week of treatment, alternate therapy should be considered.

If otorrhea persists after a full course of therapy, or if 2 or more episodes of otorrhea occur within 6 months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ciprofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species.

Spontaneous extrusion of tympanostomy tubes is not unexpected and occurred at an incidence of 1.8% in the CIPRODEX[®] treatment group in the clinical trials.

Drug Interactions

Specific drug interaction studies have not been conducted with CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension administered in the ear.

Pregnancy

Reproduction studies have been performed in rats and mice using oral doses of up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed no evidence of harm to the fetus as a result of ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. The teratogenic potential of Dexamethasone after topical (ophthalmic) treatment has been investigated in New Zealand white rabbits. Treatment with a 0.1% suspension of Dexamethasone into the conjunctival sac on days 6 through 18 of gestation resulted in a 15.6% and 32.3% incidence of fetal anomalies in two groups of rabbits.

Animal reproduction studies have not been conducted with CIPRODEX[®]. No adequate and well controlled studies have been performed in pregnant women. Caution should be exercised when CIPRODEX[®] is used by a pregnant woman.

Nursing Mothers

Ciprofloxacin and corticosteroids, as a class, appear in milk following oral administration. Dexamethasone in breast milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical otic administration of ciprofloxacin or dexamethasone could result in sufficient systemic absorption to produce detectable quantities in human milk. Because of the potential for unwanted effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the low dose used in topical otic therapy.

Pediatric Use

The safety and efficacy of CIPRODEX[®] have been established in pediatric patients 6 months and

older (937 patients) in clinical trials. In pediatric patients below the age of 6 months no data on safety and efficacy are available.

No clinically relevant changes in hearing function were observed in 69 pediatric patients (age 4 to 12 years) treated with CIPRODEX[®] and tested for audiometric parameters.

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

ADVERSE REACTIONS

In Phases II and III clinical trials, a total of 937 patients were treated with CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension. This included 400 patients with acute otitis media with otorrhea and 537 patients with acute otitis externa. The reported treatment-related adverse events are listed below:

Acute Otitis Media in pediatric patients with tympanostomy tubes

The following treatment-related adverse events occurred in 0.5% or more of the patients with non-intact tympanic membranes.

Adverse Event	Incidence (N=400)
Ear discomfort	3.0%
Ear pain	2.3%
Ear precipitate (residue)	0.5%
Irritability	0.5%
Taste perversion	0.5%

The following treatment-related adverse events were each reported in a single patient: tympanostomy tube blockage; ear pruritus; tinnitus; oral moniliasis; crying; dizziness; and erythema.

Acute Otitis Externa

The following treatment-related adverse events occurred in 0.4% or more of the patients with intact tympanic membranes.

Adverse Event	Incidence (N=537)
Ear pruritus	1.5%
Ear debris	0.6%
Superimposed ear infection	0.6%
Ear congestion	0.4%
Ear pain	0.4%
Erythema	0.4%

The following treatment-related adverse events were each reported in a single patient: ear discomfort; decreased hearing; and ear disorder (tingling).

SYMPTOMS AND TREATMENT OF OVERDOSE

There is no known treatment of overdosage since overdosage in the use of topical otic preparations is a remote possibility. Discontinue medication when heavy or protracted use is suspected.

DOSAGE AND ADMINISTRATION

SHAKE WELL IMMEDIATELY BEFORE USING

CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension contains 3mg/mL (3000µg/mL) ciprofloxacin and 1 mg/mL dexamethasone.

Acute Otitis Media in pediatric patients with tympanostomy tubes:

The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (6 months and up) through tympanostomy tubes is:

Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The suspension should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

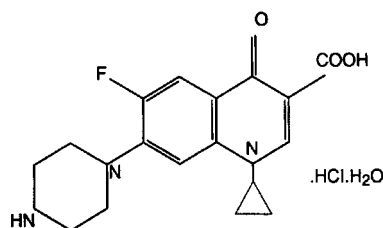
Acute Otitis Externa: The recommended dosage regimen for the treatment of acute otitis externa is:

For patients (1 year and up): Four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days. The suspension should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed.

PHARMACEUTICAL INFORMATION

Drug Substance Ciprofloxacin Hydrochloride
Proper name: Ciprofloxacin Hydrochloride
Chemical Name: 1 cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, hydrochloride monohydrate.

Structural Formula:

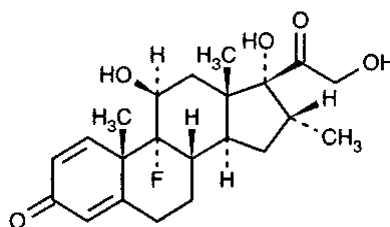


Molecular Formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular Weight: 385.8

Description: Ciprofloxacin is a faintly yellowish to light yellow crystalline substance. Ciprofloxacin is readily water soluble and the pH of a 2.5% solution is about 4.

Drug Substance Dexamethasone
Proper Name: Dexamethasone
Chemical Name: 9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione.
Structural Formula:



Molecular Formula: $C_{22}H_{29}FO_5$

Molecular Weight: 392.47

Description: Dexamethasone is a white to practically white crystalline powder, and is practically insoluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform. The melting point is about 250°C with decomposition.

Composition:

Each mL of CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension contains:

Active: Ciprofloxacin Hydrochloride (equivalent to 3 mg ciprofloxacin base) and 1 mg Dexamethasone. Preservative: 0.1 mg benzalkonium chloride. Inactive: boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium and purified water. Sodium hydroxide and/or hydrochloric acid may be added for adjustment of pH. CIPRODEX[®] has a pH of approximately 5 and an osmolality of approximately 300 mOsm/kg.

Stability and Storage Recommendations:

Store at room temperature, 15°C to 30° C. Avoid freezing. Protect from light.

AVAILABILITY:

CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension is supplied as follows: 5 mL fill and 7.5 mL fill in a DROP-TAINER[®] system. The DROP-TAINER[®] system consists of a natural polyethylene bottle and natural plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

INFORMATION FOR THE CONSUMER

CIPRODEX[®] (CI-PRO-DEX) Otic Suspension
(ciprofloxacin 0.3% and dexamethasone 0.1%)

IMPORTANT PATIENT INFORMATION AND INSTRUCTIONS. READ BEFORE USE.

What is CIPRODEX[®] ?

CIPRODEX[®] is an antibiotic/steroid combination product in a sterile suspension used to treat:

- **Middle Ear Infection with Drainage Through a Tube in Children 6 months and older:** A middle ear infection is a bacterial infection behind the eardrum. People with a tube in the eardrum may notice drainage from the ear canal.
- **Outer Ear Canal Infection in Patients 1 year and older:** An outer ear canal infection, also known as "Swimmer's Ear", is a bacterial infection of the outer ear canal. The ear canal and the outer part of the ear may swell, turn red, and be painful. Also, a fluid

discharge may appear in the ear canal.

Who should NOT use CIPRODEX[®] ?

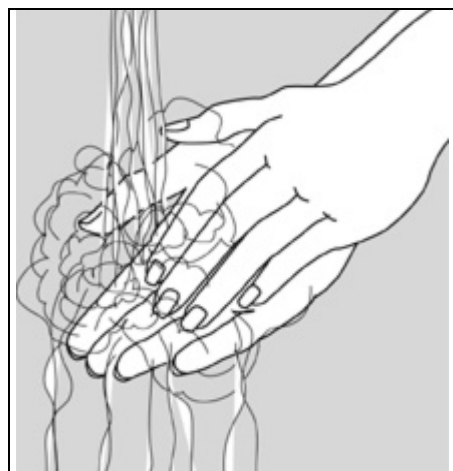
- Do not use this product if allergic to ciprofloxacin or to other quinolone antibiotics, including nalidixic acid or to any of the components in this medication (See “What does CIPRODEX[®] contain?”).
- Do not use this product if allergic to dexamethasone or to other steroids.
- Do not use this product if you have a viral infection of the external canal including herpes simplex infections.
- Do not give this product to pediatric patients who are less than 6 months old.

What does CIPRODEX[®] contain?

CIPRODEX[®] contains ciprofloxacin hydrochloride and dexamethasone as well as a preservative called benzalkonium chloride. CIPRODEX[®] also contains: boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, purified water, sodium hydroxide and/or hydrochloric acid.

How should CIPRODEX[®] be given?

1. Wash hands



The person giving CIPRODEX[®] Otic Suspension should wash his/her hands with soap and water.

2. Warm & shake bottle

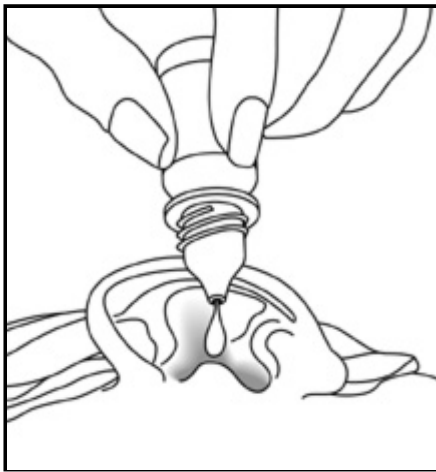


Hold the bottle of CIPRODEX[®] in the hand for one or two minutes to warm the solution, then shake well.

3. Add drops



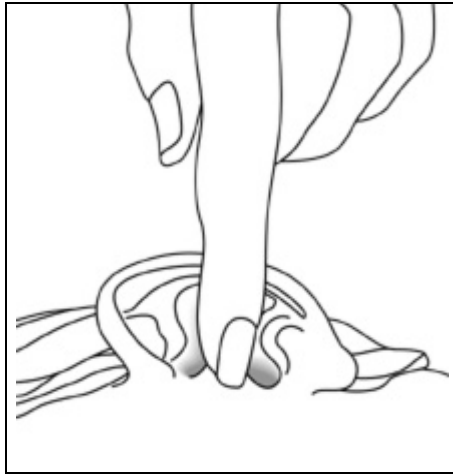
The person receiving CIPRODEX[®] should lie on his/her side with the infected ear up.



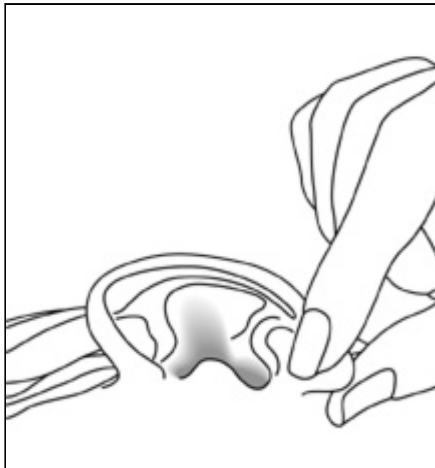
Patients should have 4 drops of CIPRODEX[®] put into the infected ear. The tip of the bottle should not touch the fingers or the ear or any other surfaces.

BE SURE TO FOLLOW INSTRUCTIONS BELOW FOR THE PATIENT'S SPECIFIC EAR INFECTION.

4. For Patients with Middle Ear Infection with Tubes: While the person receiving CIPRODEX[®] lies on his/her side, the person giving the drops should gently press the tragus (see diagram) 5 times in a pumping motion. This will allow the drops to pass through the tube in the eardrum and into the middle ear.



5. For Patients with Outer Ear Infection ("Swimmer's Ear"): While the person receiving the drops lies on his/her side, the person giving the drops should gently pull the outer ear lobe upward and backward. This will allow the ear drops to flow down into the ear canal.



6. Stay on side



The person who received the ear drops should remain on his/her side for at least 60 seconds. Repeat Steps 2-5 for the other ear if both ears are infected.

How often should CIPRODEX[®] be given?

CIPRODEX[®] ear drops should be given 2 times each day (about 12 hours apart, for example, 8 AM in the morning and 8 PM in the evening) in each infected ear unless the doctor has instructed otherwise. It is very important to use the ear drops for as long as the doctor has instructed, **even if the symptoms improve.**

What if a dose is missed?

If a dose of CIPRODEX[®] is missed, it should be given as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not use a double dose unless the doctor has instructed you to do so. If the infection is not improved after one week, you should consult your doctor. If you have two or more episodes of drainage within six months, it is recommended you see your doctor for further evaluation.

What activities should be avoided while using CIPRODEX[®] ?

It is important that the infected ear(s) remain clean and dry. When bathing, avoid getting the infected ear(s) wet. Avoid swimming unless the doctor has instructed otherwise.

What are the possible side effects of CIPRODEX® ?

During the testing of CIPRODEX® Otic Suspension for middle ear infections, the most common side effect related to CIPRODEX® was ear discomfort or ear pain that occurred in up to 3 out of 100 patients. Other common side effects were: white, flaking, scaling material in the ear; irritability; and abnormal taste. During the testing of CIPRODEX® for ear canal infections, the most common side effect related to CIPRODEX® was itching of the ear that occurred in 1 to 2 out of 100 patients. Other common side effects were: flaking and scaling material in the ear; fungus infection in the treated ear; feeling of fullness or plugging in the ear; ear pain; and skin rash. If any of these side effects continue, call the doctor. If an allergic reaction to CIPRODEX® occurs, stop using the product and contact your doctor.

DO NOT TAKE BY MOUTH

If CIPRODEX® is accidentally swallowed or overdose occurs, immediately contact your doctor or pharmacist for advice on how to proceed. Emergency care may be required. This medicine is available only with a doctor's prescription. Use only as directed. Do not use this medicine if the expiry date printed on the label has past. If you wish to learn more about CIPRODEX®, call your doctor or pharmacist.

Storage:

Store at room temperature, 15°C to 30° C. Avoid freezing. Store in carton.

Manufacturer:

Alcon Canada Inc.
Mississauga, Ontario L5N 8C7

MICROBIOLOGY

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

The following table shows the *in vitro* activity of ciprofloxacin.

Acute Otitis Media with Otorrhea

Pathogen	N	MIC range µg/mL	MIC ₅₀ µg/mL	MIC ₉₀ µg/mL
Aerobic, Gram-Positive				
<i>Staphylococcus aureus</i>	54	0.13 - 16	0.25	1.0
<i>Streptococcus pneumoniae</i>	48	0.25 - 4.0	1.0	2.0
Aerobic, Gram-Negative				
<i>Haemophilus influenzae</i>	36	0.004 - 0.13	0.008	0.016
<i>Moraxella catarrhalis</i>	11	0.013 - 0.06	0.03	0.06
<i>Pseudomonas aeruginosa</i>	48	0.06 - 2.0	0.25	0.50

Acute Otitis Externa

Pathogen	N	MIC range µg/mL	MIC ₅₀ µg/mL	MIC ₉₀ µg/mL
Aerobic, Gram-Positive				
<i>Staphylococcus aureus</i>	41	0.13 - 2.0	0.25	1.0
<i>Staphylococcus haemolyticus</i>	13	0.13 - 16	0.25	16
<i>Enterococcus faecalis</i>	29	0.50 - 2.0	1.0	2.0
Aerobic, Gram-Negative				
<i>Acinetobacter genospecies 3</i>	15	0.06 - 4.0	0.13	4.0
<i>Enterobacter aerogenes</i>	20	0.008 - 0.13	0.016	0.03
<i>Enterobacter cloacae</i>	12	0.004 - 0.03	0.016	0.03
<i>Klebsiella pneumoniae</i>	18	0.016 - 0.06	0.03	0.06
<i>Proteus mirabilis</i>	10	0.016 - 0.03	0.03	0.03
<i>Pseudomonas aeruginosa</i>	235	0.016-1.0	0.13	0.25
<i>Pseudomonas stutzeri</i>	10	0.016 - 0.25	0.13	0.25
<i>Serratia marcescens</i>	15	0.03 - 1.0	0.06	0.50

Resistance:

Cross-resistance has been observed between ciprofloxacin and other fluoroquinolones. There is generally no cross-resistance between quinolones and other classes of antibacterial agents such as β -lactams or aminoglycosides.

PHARMACOLOGY

Clinical Trials:

In a randomized, multicenter, controlled clinical trial, CIPRODEX[®] dosed 2 times per day for 7 days demonstrated clinical cures in the per protocol analysis in 86% of AOMT patients compared to 79% for ofloxacin solution, 0.3%, dosed 2 times per day for 10 days. Among culture positive patients, clinical cures were 90% for CIPRODEX[®] compared to 79% for ofloxacin solution, 0.3%. Microbiological eradication rates for these patients in the same clinical trial were 91% for CIPRODEX[®] compared to 82% for ofloxacin solution, 0.3%.

In 2 randomized multicenter, controlled clinical trials, CIPRODEX[®] dosed 2 times per day for 7 days demonstrated clinical cures in 87% and 94% of per protocol evaluable AOE patients, respectively, compared to 84% and 89%, respectively, for otic suspension containing neomycin 0.35%, polymyxin B 10,000 IU/mL, and hydrocortisone 1.0% (neo/poly/HC). Among culture positive patients clinical cures were 86% and 92% for CIPRODEX[®] compared to 84% and 89%, respectively, for neo/poly/HC. Microbiological eradication rates for these patients in the same clinical trials were 86% and 92% for CIPRODEX[®] compared to 85% and 85%, respectively, for neo/poly/HC.

TOXICOLOGY

Single-Dose Toxicity

The single-dose toxicity of ciprofloxacin has been established in several species. The oral LD₅₀ in rats and mice is > 5000 mg/kg, and about 2500 mg/kg in rabbits. Emesis in dogs and cats precluded determination of oral LD₅₀'s in these species. However, in cats it was shown to be greater than 150 mg/kg. The intramuscular LD₅₀ was >1000 mg/kg in rats and mice.

Several routes of administration have been used to determine the single-dose toxicity of dexamethasone. The oral LD₅₀ of dexamethasone in rats is > 3000 mg/kg. Subcutaneous LD₅₀'s are 14 mg/kg, 4400 mg/kg and 7200 µg/kg in rats, mice and rabbits, respectively. Intraperitoneal LD₅₀'s are 54 mg/kg in rats and 410 mg/kg in mice.

The single dose exposure to ciprofloxacin and dexamethasone from the instillation of four drops of the CIPRODEX[®] (Ciprofloxacin Hydrochloride & Dexamethasone) Otic Suspension product into the affected ear, is 0.42 mg ciprofloxacin and 0.14 mg dexamethasone. Administration of this product to a 10 kg child twice daily in both ears would result in exposures of 0.168 mg/kg ciprofloxacin and 0.056 mg/kg dexamethasone. These doses are >800 and >50,000 fold lower than the lowest oral LD₅₀'s reported for ciprofloxacin and dexamethasone, respectively. In the event that a 10 kg child should accidentally ingest the entire contents of a 7.5 ml vial of CIPRODEX[®] they would receive a dose of 2.25 mg/kg ciprofloxacin and 0.75 mg/kg dexamethasone. These doses are 66 and 4,000 fold lower than the lowest oral LD₅₀'s for ciprofloxacin and dexamethasone respectively.

Mutagenicity:

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 V₇₉ 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, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Carcinogenicity:

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species. No long term studies of CIPRODEX[®] have been performed to evaluate carcinogenic potential.

Long term studies have not been performed to evaluate the carcinogenic potential of topical otic dexamethasone. Dexamethasone has been tested for *in vitro* and *in vivo* genotoxic potential and shown to be positive in the following assays; chromosomal aberrations, sister-chromatid exchange in human lymphocytes and micronuclei and sister-chromatid exchanges in mouse bone marrow. However, the Ames/Salmonella assay, both with and without S9 mix, did not show any increase in His⁺ revertants.

Reproduction & Teratology:

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be over 1000 times the maximum recommended clinical dose of ototopical ciprofloxacin, assuming total absorption of ciprofloxacin from the ear of a 10kg child treated with CIPRODEX[®] twice per day according to label directions.

The effect of dexamethasone on fertility has not been investigated following topical otic application. However, the lowest toxic dose of dexamethasone identified following topical dermal application was 1802 µg/kg in a 26-week study in male rats and resulted in changes to the testes, epididymis, sperm duct, prostate, seminal vesicle, Cowper's gland and accessory glands. The relevance of this study for topical otic use is unknown, however this dose is > 150 fold higher than the exposure which would occur if a 50 kg adult used CIPRODEX[®] in both ears twice a day as indicated.

Local Tolerance Studies:

Guinea pigs dosed in the middle ear with CIPRODEX[®] for one month exhibited no drug-related structural or functional changes of the cochlear hair cells and no lesions in the ossicles. CIPRODEX[®] was also shown to lack dermal sensitizing potential in the guinea pig when tested according to the method of Buehler.

BIBLIOGRAPHY

1. Campoli-Richards DM, Monk JP, Price A, Benfield P, Todd PA, Ward A. Ciprofloxacin: A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1988; 35:373-447.
2. Loew D, Schuster O, and Graul E. Dose-dependent pharmacokinetics of dexamethasone. *Eur J Clin Pharmacol* 1986; 30:225-230.
3. Roland PS, Stroman DW. Microbiology of acute otitis externa. *Laryngoscope* 2002; 112:1166-1177.
4. Tsuei SE, Moore RG, Ashley JJ, McBride WG. Disposition of synthetic glucocorticoids. I. Pharmacokinetics of dexamethasone in healthy adults. *J Pharmacokinet Biopharm.* 1979; 7:249-264.
5. Roland PS, Kreisler LS, Reese B, Anon JB, Lanier B, Conroy PJ, Wall GM, Dupre SJ, Potts S, Hogg G, Stroman DW, McLean C. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. *Pediatrics* 2004; 113:40-46.

U.S. Patent Nos. 4,844,902; 6,284,804; 6,359,016

CIPRODEX[®] is a registered trademark of Bayer AG. Licensed to Alcon, Inc. by Bayer AG.