CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use XTORO safety and effectively. See full prescribing information for XTORO*

XTORO (finafloxacin otic suspension) 0.3%
For topical otic administration
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
XTORO* is a quinolone antimicrobial indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*. (1)

----------DOSAGE AND ADMINISTRATION----------
Instill four drops in the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days. (2)

----------DOSAGE FORMS AND STRENGTHS----------
5 mL of finafloxacin otic suspension, 0.3% in 8 mL bottle. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Prolonged use of this product may lead to overgrowth of nonsusceptible organisms. Discontinue use if this occurs. (5.1)
Allergic reactions may occur in patients with a history of hypersensitivity to finafloxacin, to other quinolones, or to any of the components in this medication. Discontinue use if this occurs. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions occurring in 1% of patients with XTORO were ear pruritus and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9785 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS**

**Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTORO* (finafloxacin otic suspension), 0.3% is indicated for the treatment of acute otitis externa (AOE) with or without an otowick, caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* in patients age 1 year and older.

2 DOSAGE AND ADMINISTRATION

Instill four drops into the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days.

Important administration instructions include:

- Warm the suspension by holding the bottle in the hand for one or two minutes prior to dosing in order to avoid dizziness which may result from the instillation of a cold suspension. Shake bottle well before use.
- Lie with the affected ear upward, instill the drops, and maintain the position for 60 seconds to facilitate penetration of the drops into the ear canal.
- Repeat if necessary for the opposite ear.

3 DOSAGE FORMS AND STRENGTHS

5 mL of a 0.3% topical otic suspension in an eight (8) mL bottle.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Growth of Resistant Organisms with Prolonged Use

As with other antibacterial preparations, prolonged use of XTORO (finafloxacin otic suspension) 0.3% may lead to overgrowth of nonsusceptible organisms, including yeast and fungi. If this occurs, discontinue use and institute alternative therapy.

5.2 Allergic Reactions

Allergic reactions to XTORO (finafloxacin otic suspension) 0.3% may occur in patients with a history of hypersensitivity to finafloxacin, to other quinolones, or to any of the components in this medication. If this occurs, discontinue use and institute alternative therapy.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

A total of 618 patients were treated with XTORO in two Phase 3 clinical trials. The most frequently reported adverse reactions of those exposed to XTORO occurring at an incidence of 1% included ear pruritus and nausea.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate or well-controlled studies with XTORO in pregnant women. Finafloxacin was shown to be teratogenic in rabbits and rats following oral administration. Neural tube defects and skeletal anomalies in both species, and limb anomalies in rabbits, were observed at exposures estimated to be at least 1300 times the maximum human systemic exposure following topical otic administration of 0.3% finafloxacin. Because animal studies are not always predictive of human responses, XTORO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In rabbit embryofetal studies, maternal toxicity was not observed at oral doses up to 9 mg/kg/day (estimated 8000 times the maximum human systemic exposure [0.234 ng/mL] following topical otic administration with 0.3% finafloxacin). Fetal toxicity was observed at the lowest dose tested, 1 mg/kg/day (estimated 1300 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin), and included exencephaly, enlarged fontanel, spina bifida, phocomelia, paw hyperflexure, missing lumbar vertebra, missing lumbar arch, and sternebra fusion.

In a rat embryofetal study, no adverse maternal toxicity was observed at oral doses up to 100 mg/kg/day (estimated 60,000 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin). The developmental no observed adverse effect level (NOAEL) was 30 mg/kg (estimated 22,000 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin). Exencephaly was observed in one fetus at 100 mg/kg. At 500 mg/kg, additional developmental toxicities were observed including increased preimplantation loss, decreased fetal weight, decreased placental weight, increased incidence of non-ossified sternebrae, and delayed ossifications in the sternebrae, xiphisternum, sacral arches and metacarpals.

8.3 Nursing Mothers

Finafloxacin has been identified in the milk of nursing rats following oral administration. The human systemic concentration of XTORO following topical otic treatment is low *[see CLINICAL PHARMACOLOGY (12.3)]*. It is not known whether topical otic administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Caution should be exercised when finafloxacin is administered to a nursing mother.

8.4 Pediatric Use

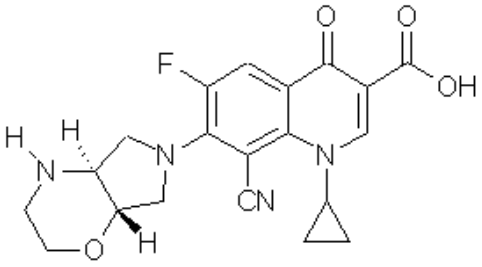
The safety and efficacy of XTORO in infants below one year of age have not been established. The safety and efficacy of XTORO in treating acute otitis externa in pediatric patients one year or older have been demonstrated in adequate and well controlled clinical trials *[see CLINICAL STUDIES 14]*.

8.5 Geriatric Use

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

11 DESCRIPTION

XTORO (finafloxacin otic suspension), 0.3% is a quinolone antimicrobial. Its chemical name is (-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4a*S*,7a*S*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6(2*H*)-y]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (CAS number 209342-40-5). Its structural formula is:



Finafloxacin has a molecular weight of 398.4. Finafloxacin is a white to yellow powder or crystals that is slightly soluble in water (0.125 mg/mL).
XTORO (finafloxacin otic suspension), 0.3% is supplied as a sterile, preserved, aqueous suspension. It has a pH of approximately 6.0 and an osmolality of approximately 290 mOsm/kg. XTORO contains **Active ingredient:** finafloxacin, 0.3%. **Preservative:** benzalkonium chloride (0.005%). **Inactive ingredients include:** sodium chloride, hydroxyethylcellulose, tyloxapol, magnesium chloride, and purified water. May contain hydrochloric acid and/or sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Finafloxacin is a fluoroquinolone antimicrobial *[see CLINICAL PHARMACOLOGY (12.4)]*.

12.3 Pharmacokinetics

Finafloxacin plasma concentrations were evaluated following single or repeated ototopical doses of XTORO (finafloxacin otic suspension), 0.3%. In healthy subjects administered 4 drops in each ear twice daily for seven days, quantifiable finafloxacin concentrations were observed in 2 of 14 subjects; and these concentrations were just above the quantitation limit (0.05 ng/mL). Similarly, in AOE patients administered a single dose of 4 or 8 drops in each ear, quantifiable finafloxacin concentrations of up to 0.234 ng/mL were observed in plasma samples from 2 of 36 AOE patients.

12.4 Microbiology

Finafloxacinbelongs to the fluoroquinolone class of antibacterials which involves the inhibition of bacterial type II topoisomerase enzymes, DNA gyrase and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

Finafloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and clinical studies as described in the INDICATIONS and USAGE section of the package insert for XTORO

Pseudomonas aeruginosa

Staphylococcus aureus.

Mechanism of Resistance

Resistance to fluoroquinolones occurs primarily by mutations in the chromosomal DNA that encode for DNA gyrase and DNA topoisomerase enzymes, decreased outer membrane permeability or drug efflux mechanisms. *In vitro* resistance to finafloxacin due to spontaneous mutation is rare.

Cross Resistance

Cross-resistance has been observed between finafloxacin and other fluoroquinolones. No cross-resistance has been observed between finafloxacin and other classes of antibacterial agents.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity

Animal studies have not been conducted to determine the carcinogenic potential of finafloxacin.

Mutagenesis

Finafloxacin was shown to be genotoxic and clastogenic *in vitro*, with and without metabolic activation, and *in vivo*. In a bacterial reverse mutation assay, finafloxacin was positive in only one strain (TA102). Finafloxacin was positive in mammalian cell culture assays: mouse lymphoma cell forward mutation assays, a mutagenicity assay in V79 Chinese hamster lung cells, and a micronucleus test in V79 cells. Finafloxacin was clastogenic in mouse micronucleus studies.

Impairment of fertility

An oral rat fertility study detected a NOAEL for male and female fertility of 100 mg/kg/day (estimated 60,000 times the maximum human systemic exposure following topical otic administration with 0.3% finafloxacin). At 500 mg/kg/day, males were completely infertile, presumably due to low sperm count and sperm immobility.

General toxicity studies in rats have confirmed sperm toxicity following oral and intravenous dosing. Following intravenous dosing, the NOAEL for sperm toxicity was 30 mg/kg/day (150,000 times the maximum human exposure following topical otic administration with 0.3% finafloxacin).

14 CLINICAL STUDIES

In two randomized multicenter, vehicle controlled clinical trials, XTORO dosed four drops twice daily for 7 days was superior to its vehicle for both clinical and microbiological outcomes as well as in time to cessation of ear pain in patients with acute otitis externa (AOE).

Among 560 patients (161 with an otowick) that were pathogen positive (baseline microbiological specimen that contained *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*), clinical cure on Day 11 was 71% in XTORO versus 37% in Vehicle. Among 1234 patients who received study treatment (Intent to Treat population (ITT)), aged 6 months to 85 years, clinical cures were 71% for XTORO and 50% in Vehicle.

Clinical Cures[a] at Day 11 (Pathogen Positive Subset, and ITT)

	Study 1			Study 2		
	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)
Pathogen + Subset	104/145 (71.7%)	46/138 (33.3%)	38.4% (27.6%, 49.1%)	101/147 (68.7%)	52/130 (40.0%)	28.7% (17.4%, 40.0%)
ITT	245/344 (71.2%)	173/342 (50.6%)	20.6% (13.5%, 27.8%)	194/274 (70.8%)	134/274 (48.9%)	21.9% (13.9%, 29.9%)

a A clinical cure was attained if the sum of the numerical scores of the 3 signs and symptoms of AOE (tenderness, erythema, and edema) was 0 at Day 11 (TOC).

The median time to cessation of ear pain in pathogen positive patients treated with XTORO was 3.5 days compared to 6.8 days in Vehicle. The median time to cessation of ear pain in ITT patients treated with XTORO was 3.5 days compared to 5.3 days in Vehicle.

Median Time (in Days) to Cessation of Ear Pain (Pathogen Positive Subset and ITT)

	Study 1			Study 2		
	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)
Pathogen + Subset	4.0	7.0	-3.0 (-5.0, -0.8)	3.0	6.5	-3.6 (-5.0, -2.0)
ITT	4.0	5.0	-1.0 (-2.0, -0.5)	3.0	5.5	-2.2 (-3.0, -1.0)

Among the pathogen positive patients, microbiological success (eradication of all baseline organisms) was achieved on Day 11 in 67% in XTORO versus 13% in the Vehicle treated patients.

Microbiological Success[b] at Day 11 (Pathogen Positive Subset)

	Study 1			Study 2		
	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)	XTORO	Vehicle	XTORO vs. Vehicle Difference (95% CI)
Pathogen + Subset	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)

b Microbiological success was attained if all pre-therapy bacteria were absent from the exit otic specimen. The presence of fungi and/or yeast was not considered in the determination of microbiological success.

In clinically cured pathogen positive patients, XTORO demonstrated eradication rates of 89% in both *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Vehicle eradication rates were 33% for *Staphylococcus aureus* and 20% for *Pseudomonas aeruginosa.*

16 HOW SUPPLIED/STORAGE AND HANDLING

XTORO (finafloxacin otic suspension) 0.3% is a sterile, preserved, aqueous, otic suspension supplied in an opaque plastic bottle with a controlled drop tip and a white cap:

5 mL fill in an 8 mL bottle (NDC 0065-XXXX-XX)

Storage and Handling
Store at 2-25°C (36-77°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Allergic Reactions:
Advise patients that if a rash or allergic reaction occurs, they should discontinue the use of the product immediately and contact their physician.

Warm the Bottle in Hands Before Use:
Advise patients or caregivers that prior to administration of XTORO, they should warm the bottle by holding it in their hands for one or two minutes to avoid dizziness which may result from the instillation of a cold solution.

For Use with an Otowick:
Advise patients that following instillation of 8 drops at the time of otowick insertion, they should continue with the lower dose of 4 drops administered twice daily for seven days.

Revised: December 2014
U.S. Patents Nos: 6,133,206; 6,432,948; 8,536,167

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F.P.O.

PATIENT INFORMATION

Xtoro®
(finafloxacin otic suspension) 0.3%

For use in the ear.
Read the Patient Information that comes with Xtoro Otic Suspension carefully before you start using it. This leaflet does not take the place of talking to your health care provider about your medical condition or your treatment.

What is Xtoro® (finafloxacin otic suspension) 0.3%?
Xtoro Otic Suspension is a prescription medicine that is used to treat bacterial infections of the external ear canal in adults and children 1 year and older.

What should I tell my health care provider before taking Xtoro® (finafloxacin otic suspension) 0.3%?

Tell your healthcare provider about all your medical conditions, including if you are:

- allergic to any antibacterials including fluoroquinolones or to any of the ingredients in Xtoro Otic Suspension. See the end of this leaflet for a complete list of the ingredients in Xtoro Otic Suspension.
- pregnant or planning to become pregnant. It is not known if Xtoro Otic Suspension will harm your unborn baby.
- breast-feeding a baby. It is not known if Xtoro Otic Suspension passes into your breast milk.

Tell your health care provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products. Xtoro Otic Suspension and other medicines may affect each other, causing side effects.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I use Xtoro® (finafloxacin otic suspension) 0.3%?

- Xtoro Otic Suspension is for use in the ear. **Do not drop it in your eyes or mouth.**
- Do not give this product to children less than 1 year old.
- Use Xtoro Otic Suspension exactly as your healthcare provider tells you. Do not stop taking Xtoro Otic Suspension without talking to your healthcare provider.
- The bottle, and any remaining product, should be discarded after the prescribed therapy or after the expiration date on the medicine label or box.

Follow the Patient Instructions for Use below.

What are the possible side effects of Xtoro® (finafloxacin otic suspension) 0.3%?

Side effects of Xtoro® (finafloxacin otic suspension) 0.3% include:

- itching in the ear canal
- nausea

Tell your healthcare provider if you have any side effects that bother you or do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-757-9195.

What should I avoid while using Xtoro® (finafloxacin otic suspension)?

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

General Information about Xtoro® (finafloxacin otic suspension) 0.3%

Do not use Xtoro Otic Suspension for a condition for which it was not prescribed. Do not give Xtoro Otic Suspension to other people, even if they have the same conditions as you. It may harm them. This patient leaflet summarizes the most important information about Xtoro Otic Suspension. If you would like more information about Xtoro Otic Suspension talk with your healthcare provider. You can ask your healthcare provider or pharmacist about Xtoro Otic Suspension that is written for healthcare professionals.

What are the ingredients of Xtoro® (finafloxacin otic suspension) 0.3%?

Active ingredients: finafloxacin 3 mg
Inactive ingredients: tyloxapol, hydroxyethyl cellulose, sodium chloride, magnesium chloride, benzalkonium chloride (as preservative) and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

What should I know about Acute Otitis Externa (Swimmers Ear)?

Acute Otitis Externa, an ear canal infection, also known as "Swimmers Ear", is a bacterial infection of the outer ear canal. The ear canal and outer part of the ear may swell, turn red, and be painful. Also, a fluid discharge may appear in the outer ear canal. Your physician may place an otowick in your ear to help deliver Xtoro to the area of infection.

Revised: November 2014
U.S. Patent Nos: 6,133,206; 6,432,948; 8,536,167

Manufactured By:
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AAA4508-1113

F.P.O.

PHARMACIST Give To Patient

PATIENT INSTRUCTIONS FOR USE

Xtoro®
(finafloxacin otic suspension) 0.3%

Rx Only

STERILE **For use in the ear**

It is best if another person can put the drops in for you. Children should never be allowed to put the drops in themselves.

1. Wash hands
The person giving Xtoro® Otic Suspension should wash his/her hands with soap and water.

2. Warm & shake the bottle
The person giving Xtoro should hold the bottle in their hand(s) for one or two minutes to warm the suspension

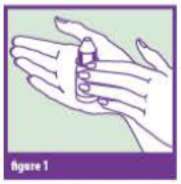


figure 1

(figure 1) to avoid the dizziness that may result from the instillation of a cold suspension into the ear canal, then shake the bottle well before use.

3. Add drops
The person receiving Xtoro® should lie on his/her side with the infected ear up (figure 2).


figure 2

Patient should have **4 drops** of Xtoro put into the infected ear (figure 3). If otowick is in place, patient should have 4 drops of Xtoro put into the infected ear at the surface of the otowick. **Do not touch** the ear, fingers or any other surfaces **with the tip of the bottle** as it could contaminate the drops.


figure 3

4. Pull Lobe
While the patient lies on his/her side, the person giving Xtoro® should gently pull the outer ear lobe upward and backward (figure 4). This will allow the ear drops to flow down into the ear canal.


figure 4

5. Stay on side
The patient should remain on his/her side for at least 60 seconds.

Repeat Steps 3-5 for the other ear if both ears are infected.

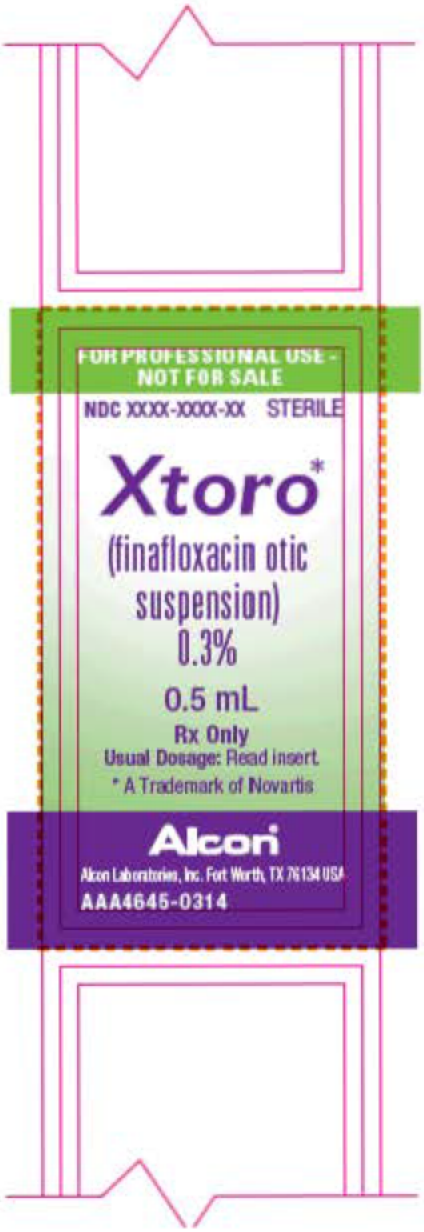
Alcon
a Novartis company

Container Labels

Professional sample size: 0.5 mL fill in a 4 mL bottle

Trade size: 5 mL fill in an 8 mL bottle

U.S. Sticker 0.5 mL Sample



Carton Labels

Professional sample size: 0.5 mL fill in a 4 mL bottle

Trade size: 5 mL fill in an 8 mL bottle

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/s/

JOHN J FARLEY
12/17/2014