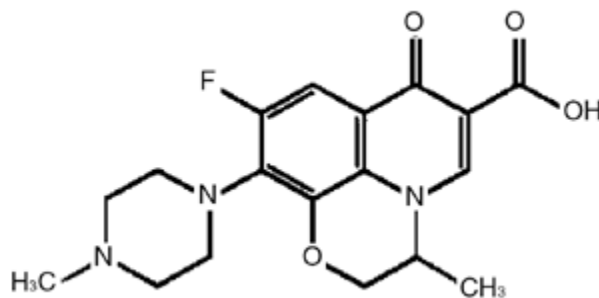


FLOXIN® Otic

(ofloxacin otic solution 0.3%)

DESCRIPTION:

FLOXIN® Otic (ofloxacin otic solution) 0.3% is a sterile aqueous anti-infective (anti-bacterial) solution for otic use. Chemically, ofloxacin has three condensed 6-membered rings made up of a fluorinated carboxyquinolone with a benzoxazine ring. The chemical name of ofloxacin is: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The empirical formula of ofloxacin is C₁₈H₂₀FN₃O₄ and its molecular weight is 361.38. The structural formula is:



FLOXIN® Otic contains 0.3% (3mg/ml) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5 .

CLINICAL PHARMACOLOGY

Pharmacokinetics: Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two single-dose studies, mean ofloxacin serum concentrations were low in adult patients with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1 ng/ml (n=3) and 5.4 ng/ml (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level of ofloxacin

detected was 10 ng/ml after administration of a 0.3% solution. Ofloxacin was detectable in the middle ear mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2 to 602 µg/g after otic administration of a 0.3% solution. Ofloxacin was present in high concentrations in otorrhea (389 - 2850 µg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with chronic suppurative otitis media and perforated tympanic membranes. However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

Microbiology: Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus

Streptococcus pneumoniae

Aerobic and facultative gram-negative microorganisms:

Escherichia coli

Haemophilus influenzae

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

INDICATIONS AND USAGE:

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Otitis Externa in adults and pediatric patients, 6 months and older, due to *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

CONTRAINDICATIONS

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR OPHTHALMIC USE.

NOT FOR INJECTION.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

PRECAUTIONS

General: As with other anti-infective preparations, prolonged use may result in over-growth of nonsusceptible organisms, including fungi. If the infection is not improved after one week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin 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.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

Information for Patients: Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Otitis Externa

Prior to administration of FLOXIN[®] Otic, the solution 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 solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for five minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Acute Otitis Media and Chronic Suppurative Otitis Media

Prior to administration of FLOXIN[®] Otic, the solution 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 solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: Specific drug interaction studies have not been conducted with FLOXIN[®] Otic.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted. Ofloxacin was not mutagenic in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micronucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with FLOXIN[®] Otic twice per day.

Pregnancy

Teratogenic effects: Pregnancy Category C. Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

Nonteratogenic Effects: Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. FLOXIN[®] Otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin 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.

Pediatric Use: Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- six months and older: otitis externa with intact tympanic membranes
- one year and older: acute otitis media with tympanostomy tubes
- twelve years and older: chronic suppurative otitis media with perforated tympanic membranes.

Safety and efficacy in pediatric patients below these ages have not been established.

Although no data are available on patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.

Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

ADVERSE REACTIONS

Subjects with Otitis Externa

In the phase III clinical trials performed in support of once-daily dosing, 799 subjects with otitis externa and intact tympanic membranes were treated with ofloxacin otic solution. The studies, which served as the basis for approval, were 020 (pediatric, adolescents and adults), 016 (adolescents and adults) and 017 (pediatric). The following treatment-related adverse events occurred in two or more of the subjects.

| Adverse Event | Incidence Rate | | |
|---------------------------|--|---|---|
| | Studies 002/003 [†] BID (N=229) | Studies 016/017 [†] QD (N=310) | Study 020 [†] QD (N=489) |
| Application Site Reaction | 3% | 16.8% | 0.6% |
| Pruritus | 4% | 1.2% | 1.0% |
| Earache | 1% | 0.6% | 0.8% |
| Dizziness | 1% | 0.0% | 0.6% |
| Headache | 0% | 0.3% | 0.2% |

| | | | |
|---------|----|------|------|
| Vertigo | 1% | 0.0% | 0.0% |
|---------|----|------|------|

† Studies 002/003 (BID) and 016/017 (QD) were active-controlled and comparative. Study 020 (QD) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) and Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes

In phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution:

| <u>Adverse Event</u> | <u>Incidence (N=656)</u> |
|----------------------|--------------------------|
| Taste Perversion | 7% |
| Earache | 1% |
| Pruritus | 1% |
| Paraesthesia | 1% |
| Rash | 1% |
| Dizziness | 1% |

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single

subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

Post-marketing Adverse Events

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

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

For pediatric patients (from 6 months to 13 years old): Five drops (0.25 ml, 0.75 mg ofloxacin) instilled into the affected ear once daily for seven days.

For patients 13 years and older: Ten drops (0.5 ml, 1.5 mg ofloxacin) instilled into the affected ear once daily for seven days.

The solution 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 solution. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for five minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

Acute Otitis Media in pediatric patients with tympanostomy tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from 1 to 12 years old) with tympanostomy tubes is:

Five drops (0.25 ml, 0.75 mg ofloxacin) instilled into the affected ear twice daily for ten days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness that may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

Chronic Suppurative Otitis Media with perforated tympanic membranes: The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is:

Ten drops (0.5 ml, 1.5 mg ofloxacin) instilled into the affected ear twice daily for fourteen days. The solution should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness that may result from the instillation of a cold solution. The patient should lie with the affected ear upward, before instilling the drops. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

HOW SUPPLIED

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is supplied in plastic dropper bottles containing 5 ml and 10 ml. The NDC codes are:

63395-101-05 FLOXIN[®] Otic 5ml

63395-101-10 FLOXIN[®] Otic 10 ml

Store at 15- 25° C (59 - 77° F).

Rx Only

Daiichi Pharmaceutical Corporation

Montvale, NJ 07645

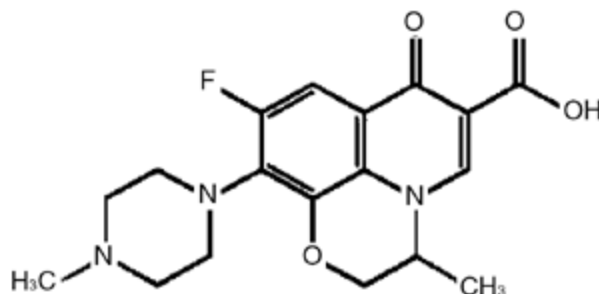
Revised (September, 2003)

Covered by U.S. Patent No. 5,401,741.

FLOXIN® Otic (ofloxacin otic solution 0.3%)

DESCRIPTION:

FLOXIN® Otic (ofloxacin otic solution) 0.3% is a sterile aqueous anti-infective (anti-bacterial) solution for otic use. Chemically, ofloxacin has three condensed 6-membered rings made up of a fluorinated carboxyquinolone with a benzoxazine ring. The chemical name of ofloxacin is: (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The empirical formula of ofloxacin is $C_{18}H_{20}FN_3O_4$ and its molecular weight is 361.38. The structural formula is:



FLOXIN® Otic contains 0.3% (3mg/ml) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5 .

CLINICAL PHARMACOLOGY

Pharmacokinetics: Drug concentrations in serum (in subjects with tympanostomy tubes and perforated tympanic membranes), in otorrhea, and in mucosa of the middle ear (in subjects with perforated tympanic membranes) were determined following otic administration of ofloxacin solution. In two single-dose studies, mean ofloxacin serum concentrations were low in adult patients with tympanostomy tubes, with and without otorrhea, after otic administration of a 0.3% solution (4.1 ng/ml (n=3) and 5.4 ng/ml (n=5), respectively). In adults with perforated tympanic membranes, the maximum serum drug level of ofloxacin detected was 10 ng/ml after administration of a 0.3% solution. Ofloxacin was detectable in the middle ear

mucosa of some adult subjects with perforated tympanic membranes (11 of 16 subjects). The variability of ofloxacin concentration in middle ear mucosa was high. The concentrations ranged from 1.2 to 602 µg/g after otic administration of a 0.3% solution. Ofloxacin was present in high concentrations in otorrhea (389 - 2850 µg/g, n=13) 30 minutes after otic administration of a 0.3% solution in subjects with chronic suppurative otitis media and perforated tympanic membranes. However, the measurement of ofloxacin in the otorrhea does not necessarily reflect the exposure of the middle ear to ofloxacin.

Microbiology: Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its antibacterial activity by inhibiting DNA gyrase, a bacterial topoisomerase. DNA gyrase is an essential enzyme which controls DNA topology and assists in DNA replication, repair, deactivation, and transcription. Cross-resistance has been observed between ofloxacin and other fluoroquinolones. There is generally no cross-resistance between ofloxacin and other classes of antibacterial agents such as beta-lactams or aminoglycosides.

Ofloxacin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in otic infections as described in the **INDICATIONS AND USAGE** section.

Aerobic and facultative gram-positive microorganisms:

Staphylococcus aureus

Streptococcus pneumoniae

Aerobic and facultative gram-negative microorganisms:

Escherichia coli

Haemophilus influenzae

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

INDICATIONS AND USAGE:

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

Otitis Externa in adults and pediatric patients, 6 months and older, due to *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

CONTRAINDICATIONS

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is contraindicated in patients with a history of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS

NOT FOR OPHTHALMIC USE.

NOT FOR INJECTION.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones, including ofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to ofloxacin is suspected, stop the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management, including intubation, should be administered as clinically indicated.

PRECAUTIONS

General: As with other anti-infective preparations, prolonged use may result in over-growth of nonsusceptible organisms, including fungi. If the infection is not improved after one week, cultures should be obtained to guide further treatment. If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

The systemic administration of quinolones, including ofloxacin 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.

Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.

No signs of local irritation were found when 0.3% ofloxacin was applied topically in the rabbit eye. Ofloxacin was also shown to lack dermal sensitizing potential in the guinea pig maximization study.

Information for Patients: Avoid contaminating the applicator tip with material from the fingers or other sources. This precaution is necessary if the sterility of the drops is to be preserved. Systemic quinolones, including ofloxacin, have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Otitis Externa

Prior to administration of FLOXIN[®] Otic, the solution should be warmed by holding the single-dispensing container(s) in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. This position should be maintained for five minutes to facilitate penetration of the medication into the ear canal. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Acute Otitis Media and Chronic Suppurative Otitis Media

Prior to administration of FLOXIN[®] Otic, the solution should be warmed by holding the single-dispensing container(s) in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions: Specific drug interaction studies have not been conducted with FLOXIN[®] Otic.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted. Ofloxacin was not mutagenic in the Ames test, the sister chromatid exchange assay (Chinese hamster and human cell

lines), the unscheduled DNA synthesis (UDS) assay using human fibroblasts, the dominant lethal assay, or the mouse micronucleus assay. Ofloxacin was positive in the rat hepatocyte UDS assay, and in the mouse lymphoma assay. In rats, ofloxacin did not affect male or female reproductive performance at oral doses up to 360 mg/kg/day. This would be over 1000 times the maximum recommended clinical dose, based upon body surface area, assuming total absorption of ofloxacin from the ear of a patient treated with FLOXIN[®] Otic twice per day.

Pregnancy

Teratogenic effects: Pregnancy Category C. Ofloxacin has been shown to have an embryocidal effect in rats at a dose of 810 mg/kg/day and in rabbits at 160 mg/kg/day.

These dosages resulted in decreased fetal body weights and increased fetal mortality in rats and rabbits, respectively. Minor fetal skeletal variations were reported in rats receiving doses of 810 mg/kg/day. Ofloxacin has not been shown to be teratogenic at doses as high as 810 mg/kg/day and 160 mg/kg/day when administered to pregnant rats and rabbits, respectively.

Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses.

Nonteratogenic Effects: Additional studies in the rat demonstrated that doses up to 360 mg/kg/day during late gestation had no adverse effects on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. There are, however, no adequate and well-controlled studies in pregnant women. FLOXIN[®] Otic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: In nursing women, a single 200 mg oral dose resulted in concentrations of ofloxacin in milk which were similar to those found in plasma. It is not known whether ofloxacin is excreted in human milk following topical otic administration. Because of the potential for serious adverse reactions from ofloxacin 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.

Pediatric Use: Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications:

- six months and older: otitis externa with intact tympanic membranes.

- one year and older: acute otitis media with tympanostomy tubes.
- twelve years and older: chronic suppurative otitis media with perforated tympanic membranes.

Safety and efficacy in pediatric patients below these ages have not been established.

Although no data are available on the patients less than age 6 months, there are no known safety concerns or differences in the disease process in this population that will preclude use of this product.

No changes in hearing function occurred in 30 pediatric subjects treated with ofloxacin otic and tested for audiometric parameters.

Although quinolones, including ofloxacin, have been shown to cause arthropathy in immature animals after systemic administration, young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution for one month showed no systemic effects, quinolone-induced lesions, erosions of the cartilage in weight-bearing joints, or other signs of arthropathy.

ADVERSE REACTIONS

Subjects with Otitis Externa

In the phase III clinical trials performed in support of once-daily dosing, 799 subjects with otitis externa and intact tympanic membranes were treated with ofloxacin otic solution. The studies, which served as the basis for approval, were 020 (pediatric, adolescents and adults), 016 (adolescents and adults) and 017 (pediatric). The following treatment-related adverse events occurred in two or more of the subjects.

| Adverse Event | Incidence Rate | | |
|---------------------------|--|---|---|
| | Studies 002/003 [†] BID (N=229) | Studies 016/017 [†] QD (N=310) | Study 020 [†] QD (N=489) |
| Application Site Reaction | 3% | 16.8% | 0.6% |
| Pruritus | 4% | 1.2% | 1.0% |
| Earache | 1% | 0.6% | 0.8% |
| Dizziness | 1% | 0.0% | 0.6% |
| Headache | 0% | 0.3% | 0.2% |
| Vertigo | 1% | 0.0% | 0.0% |

[†] Studies 002/003 (BID) and 016/017 (QD) were active-controlled and comparative. Study 020 (QD) was open and non-comparative.

An unexpected increased incidence of application site reaction was seen in studies 016/017 and was similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone).

This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

In once daily dosing studies, there were also single reports of nausea, seborrhea, loss of hearing, tinnitus, otitis externa, otitis media, tremor, hypertension and fungal infection.

In twice daily dosing studies, the following treatment-related adverse events were each reported in a single subject: dermatitis, eczema, erythematous rash, follicular rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing and otorrhagia.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) and Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes

In phase III clinical trials which formed the basis for approval, the following treatment-related adverse events occurred in 1% or more of the 656 subjects with non-intact tympanic membranes in AOM TT or CSOM treated twice-daily with ofloxacin otic solution:

| Adverse Event | Incidence (N=656) |
|------------------|-------------------|
| Taste Perversion | 7% |
| Earache | 1% |
| Pruritus | 1% |
| Paraesthesia | 1% |
| Rash | 1% |
| Dizziness | 1% |

Other treatment-related adverse reactions reported in subjects with non-intact tympanic membranes included: diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.6%), tinnitus (0.3%), fever (0.3%). The following treatment-related adverse events were each reported in a single

subject: application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

Post-marketing Adverse Events

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-

marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

DOSAGE AND ADMINISTRATION

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

For pediatric patients (from 6 months to 13 years old): instill the contents of 1 single-dispensing container into the affected ear once daily for seven days.

For patients 13 years and older: instill the contents of 2 single-dispensing containers into the affected ear once daily for seven days.

The solution should be warmed by holding the container in the hand for one or two minutes to avoid dizziness which may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. This position should be maintained for five minutes to facilitate penetration of the medication into the ear canal. Repeat, if necessary, for the opposite ear.

Acute Otitis Media in pediatric patients with tympanostomy tubes: The recommended dosage regimen for the treatment of acute otitis media in pediatric patients (from 1 to 12 years old) with tympanostomy tubes is:

Instill the contents of 1 single-dispensing container into the affected ear twice daily for ten days.

The solution should be warmed by holding the container in the hand for one or two minutes to avoid dizziness that may result from the instillation of a cold solution. The patient should lie with the affected ear upward, and then the medication should be instilled. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear.

This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

Chronic Suppurative Otitis Media with perforated tympanic membranes: The recommended dosage regimen for the treatment of chronic suppurative otitis media with perforated tympanic membranes in patients 12 years and older is:

Instill the contents of 2 single-dispensing containers into the affected ear twice daily for fourteen days. The solution should be warmed by holding the container in the hand for one or two minutes to avoid dizziness that may result from the instillation of a cold solution. The patient should lie

with the affected ear upward, before instilling the medication. The tragus should then be pumped 4 times by pushing inward to facilitate penetration into the middle ear. This position should be maintained for five minutes. Repeat, if necessary, for the opposite ear.

HOW SUPPLIED

FLOXIN[®] Otic (ofloxacin otic solution) 0.3% is supplied in plastic single-dispensing containers, 0.25 mL each. The NDC codes are:

63395-101-01 FLOXIN[®] Otic 2 single-dispensing containers, 0.25 mL each Professional Sample

63395-101-11 FLOXIN[®] Otic 20 single-dispensing containers, 0.25 mL each

Store at 15- 25° C (59 - 77° F).

Rx Only

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