

# Liability Jitters May Impede Patient Safety System

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WASHINGTON — The patient safety system signed into law this summer by President Bush will likely take many months to implement; but, after operating so long in an environment of liability fear, doctors may take even longer to trust it, said Michael O. Fleming, M.D., board chair of the American Academy of Family Physicians.

"I think physicians are going to have to get comfortable with this and realize that [documenting errors under the plan] is a thing that you can do now, and it's going to improve quality tremendously," said Dr. Fleming. But, he added, it may take physicians some time to lose their reporting inhibitions.

Doctors are concerned about reporting something going wrong, because someone will be at fault and liable for that situation, he said. "In medicine, unfortu-

nately, too many times everybody—from staff to nurses to doctors—has been afraid to report things."

Under the new law, a "patient safety work product" of reported errors and near misses is privileged and cannot be used in legal or disciplinary actions. Data collected can only be used in a criminal trial after the court makes a determination that the evidence is "material to the proceeding" and "not reasonably available from another source," according to text of

the Patient Safety and Quality Improvement Act of 2005.

The structure will allow providers to voluntarily submit information to patient safety organizations certified by the Health and Human Services department. Patient confidentiality must be maintained. The purpose of the system is to create a searchable database of medical errors that can be analyzed and used to develop new care systems and best practices that would avoid similar errors in the future.

Dr. Fleming said the arrangement could help reveal weaknesses in medication dispensing and other systems. "This will give us an opportunity, when these errors occur, to report them without having to worry about the consequences of a liability threat," he noted.

The law became effective when the president signed it and authorizes federal funding for fiscal years 2006-2010. Implementation could begin as early as next year, said Gordon Wheeler, associate executive director for public affairs for the American



DAIICHI PHARMACEUTICAL CORPORATION

## FLOXIN® Otic

(ofloxacin otic) solution 0.3%

**Brief Summary.** Please see product insert for complete prescribing information.

### 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 non-susceptible 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, transient 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, hypoesthesia, 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): 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 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.

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

Rx Only

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DR. FLEMING

College of Emergency Physicians, noting that for that to happen, the HHS "secretary's got a lot to do to set it up."

HHS must coordinate databases nationwide into a single aggregated interactive resource for providers and patient safety organizations (PSOs). It also must develop or adopt voluntary national standards to promote the electronic exchange of health care information. HHS will also certify the PSOs.

According to Margaret VanAmringe, vice president for public policy and government relations at the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), there are several possible models for the PSOs including U.S. Pharmacopeia's MEDMARX system. For a subscription fee, hospitals and health care systems can access MEDMARX's database to track adverse drug reactions and medication errors.

AAFP's Dr. Fleming said that while many PSOs likely would be run by systems analysts and industrial engineers, "I'm hoping there are also going to be peers." He added, "I think physicians are going to feel much more comfortable if we have peer evaluation."

Ms. VanAmringe said PSOs will not only need to collect data but also have the ability to aggregate and analyze those data to provide institutions with "feedback on common problems." They will develop solutions and best practices by collating data from different institutions and then monitoring whether proposed interventions work.

"PSOs will play a fairly robust role in using the data that are reported to them," she said.

